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AN AMERICAN TEXT-BOOK OF PATHOLOGY

FOR THE USE OF STUDENTS
AND PRACTITIONERS OF
MEDICINE AND SURGERY

EDITED BY

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PREFACE.

THE present volume is the outcome of a desire on the part of the editors and the publishers to place in the hands of the medical student and the physician a comprehensive text-book upon the essential principles and facts in General Pathology and Pathologic Anatomy. Pathology has made such enormous strides in recent years that it is almost an impossibility for one man to make himself fully conversant with the entire field of knowledge in this important branch of science. Realizing this, the editors have endeavored to secure for each of the major departments the services of one who is thoroughly familiar with the particular subject, and can best put the theories and conclusions in an authoritative form. Each writer has been left a large share of freedom in utilizing the material at his hand, so as not to dwarf all individuality—a feature which the editors trust will commend itself to the reader. In this fact lies the explanation why, for instance, references to the literature are more frequent in some articles than in others.

The editors wish to thank heartily all the collaborators in the preparation of this book for their earnest efforts to make the work thorough and useful, and a worthy exponent of the great subject with which it deals. To Dr. John Guitéras, who, previous to his removal to Havana, had taken an editorial interest in the book, the editors are indebted for the privilege of using a number of excellent illustrations. They also desire to express their sincere appreciation of the valuable assistance and patient cooperation of the publishers.

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GENERAL PATHOLOGY.

INTRODUCTION.

HEALTH AND DISEASE.

THE human body consists of cells and of intercellular substances derived from the cells. In the different parts of the body cells of very different appearance and function are met with ; thus we speak of epithelial cells, nerve-cells, muscle-cells, bone-cells, cartilage-cells, blood-cells, connective-tissue cells. Portions of the body made up chiefly of one variety of cells constitute a *tissue* ; the epidermis is an epithelial tissue, as is also the lining of the alimentary tract ; the skeleton consists in part of bony tissue, in part of cartilaginous tissue ; the heart is made up chiefly of muscular tissue ; the skull is filled mainly with nerve-tissue. Tissues of various sorts are combined in different ways to form *organs* ; the liver is made up of epithelial tissue, combined with connective tissue, vascular tissue, muscular tissue, and nerve-tissue ; the intestine is composed of epithelial tissue, connective tissue, blood- and lymph-vessels, muscular tissue, and nerve-tissue. All the cells composing the various organs and their constituent tissues have been derived from a single cell—the fertilized egg-cell. Formed by the fusion of a single spermatozoon with a single ovum, this fertilized egg-cell represents the sum of the substances and forces derived primarily from the two parents ; that is to say, it is the substratum of the phenomena which we include under the term *heredity*. The fertilized egg-cell lodged upon a normal uterine mucous membrane and finding there conditions favorable to its development, begins to undergo subdivision first into two cells, then into four, eight, sixteen, and later into an enormous number of cells. In its development the fertilized egg-cell—in this case the human organism—is greatly dependent upon and markedly influenced by substances and forces from without it. Not only is this true while the organism remains within the uterine cavity of the mother, but also after it has reached the world outside of the mother. The influences which affect the organism from without are designated *influences of environment*. As far as can at present be seen, the structure and functions of every human organism have to be regarded as the exact resultant of the interplay of inherited substances and forces with the substances and forces in the environment of the organism.

In all probability no two human beings are exactly alike, for in the first place all evidence is in favor of the view that the individual spermatozoa of a given male as well as the individual ova of a given female differ materially from one another ; and in the second place, the influences of environment, though sometimes nearly, are never exactly equivalent for two individuals. It is surprising, not that human beings are so different from one another as they are, but rather that they resemble one another in structure and function so closely as we find that they do.

If it be true that all individuals differ more or less from one another, the

difficulties of arriving at a decision as to what is to be regarded as the *normal* individual becomes obvious. The questions "What is health?" and "What is disease?" have been frequently asked, and, it must be confessed, without receiving wholly satisfactory answers. When we begin to form abstract conceptions of an ideal human being we always arrive at mental pictures inconsonant with reality, because demanding conditions of heredity and environmental influence at present unattainable. In medicine, however, we have to deal with real human beings, not ideal ones; and accordingly medical writers have agreed to take the *average* of a large series of observations of structure and function made on human beings who by common consent are regarded as healthy individuals as a standard of the normal, and to regard as abnormal only those deviations from that standard which exceed a certain limit. Thus far the data for the construction of the normal standard of the whole body are insufficient, for to have these it is necessary that the normal standard for all the various organs be determined. The way has been indicated by Thoma.¹ As an example, his study of the weight of the two kidneys in healthy individuals of thirty-five years of age may be instanced. In 200 observations the weight was found to vary between 121 and 491 grams; the arithmetic mean of all the observations was 306 grams. According to the theory of probabilities, 306 grams may therefore be regarded as the most probable weight of the kidneys of a healthy individual thirty-five years old. Of the individual deviations from this weight, half of the 200 observations were contained within the limits 269 ($306-37$) grams and 343 ($306+37$) grams. Accordingly, in half of the cases the individual deviations in weight do not amount to more than 37 grams, which may therefore be regarded as the probable standard of individual deviation for the weight of the healthy kidneys at thirty-five years of age. If a normal standard were established for all the structural and functional relations of the body, a normal for the whole body could be set up. Very marked deviations from this normal, exceeding individual anatomic and physiologic deviations in conditions of health, would have to be regarded as morbid or pathologic, and we could then empirically define disease, as Thoma suggests, as a deviation from the normal in the anatomic or chemical structure, or in the functions of the body, its organs and elements of organs, which exceeds the limits of individual physiologic variation. But, as the author of the suggestion admits, such a definition gives no explanation of the nature of disease; it does no more than give the criteria for deciding when any condition is to be called pathologic. Of the many attempts to define disease more fully, none is wholly satisfactory. Chomel's definition is very frequently cited: "Disease is a notable disorder affecting either the material disposition of the constituent parts of the living body or the exercise of their functions," as is also that of Monneret, "Disease is an abnormal state of the living body, characterized by an alteration of structure or by a disturbance of function."

Since the idea of a peculiar "vital force" has been superseded by the conception of "specific cellular activities," the conception has been gaining ground that no hard and fast line can be drawn between normal and pathologic processes. The activities of cells are subject to certain definite laws, which hold in diseased conditions of the body as well as in health. When

¹ Thoma, R., *Untersuchungen ueber die Grösse und das Gewicht der anatomischen Bestandtheile des menschlichen Körpers im gesunden und kranken Zustande*, Leipzig, 1882.

the structure or function of an organism differs markedly from a normal standard for the species, the reason lies either in the abnormality of the inherent activities of some or all of the cells of the organism, or in the abnormal nature of the environmental influences to which some or all of the cells are exposed, or in both. In any of these cases morbid instead of normal reactions are encountered. In the first instance environmental influences, normal for healthy individuals, would call forth morbid reactions; in the second instance individuals previously healthy would become diseased through environmental influences which are incompatible with the maintenance of health because outside the ordinary deviations from the average; and in the third instance the two conditions would be combined.

PATHOLOGY AND ITS SUBDIVISIONS.

The science which studies diseased or abnormal conditions is called *pathology* (πάθος, disease; λόγος, an account of). So extensive a field is included in this term that the science is conveniently divided into several departments. In the first place, it is customary to distinguish General Pathology from Special, or Descriptive, Pathology. By the latter is understood the science which deals with the abnormal conditions in individual diseases; it analyzes the cause or causes of each individual disease, the mode in which the cause leads to morbid reactions on the part of the cells, the structural and functional alterations which are ascertainable, and the course and termination of the disease. It is by no means confined to a study of the postmortem lesions to be found in cases of disease; on the contrary, it deals especially with the phenomena observable during life.

Special pathology is commonly subdivided into *medical*, or *internal*, *pathology*, and *surgical*, or *external*, *pathology*, the former dealing with the deeper and more concealed organs, the latter with those easily accessible. But the domains of medicine and surgery are more and more overlapping one another, so that no strict line can be drawn between the two, and the arbitrary subdivision is simply a matter of convenience. The same is true of the finer subdivisions of special pathology—dermatology, ophthalmology, rhinology, laryngology, gynecology, and the like.

General pathology stands in the same relation to special pathology that philosophy occupies as regards the individual sciences; it is the synthesis of the analyses which special pathology affords. It strives to find out the laws which govern disease in general, searches for the causes of disease, discovers the order of events in diseased conditions, and groups the symptoms and lesions common to whole series of special pathologic processes. It has less to do with the collection of individual facts and observations than with their arrangement and explanation.

Pathologic anatomy deals with the structural alterations or *lesions* observable in diseased conditions of the organism, not only with those which can be made out with the naked eye (*gross morbid anatomy*), but also those ascertainable with the aid of the microscope (*minute morbid anatomy* or *pathologic histology*).

Pathologic physiology studies the deviations of the functions of the organism from the normal under pathologic conditions; in other words, it investigates "morbid reactions."

Pathologic chemistry and physics have to deal with the devia-

tions in the constitution of the substances of which the body is composed and in the nature and disposition of the forces at work in the organism when it is diseased.

That part of pathology which has to do with the causes of disease is known as *etiology* (*αἰτία*, cause; *λόγος*, an account of). The province of *pathogeny* or *pathogenesis* (*πάθος*, disease; *γένεσις*, generation) is to trace the sequence of events from the beginning of the action of the causative agent to the period when the disease has reached its full development.

Human pathology is concerned with the study of diseased human beings only, while *comparative pathology* investigates the processes of disease in animals other than human beings. *Experimental pathology* attempts to throw light upon the phenomena of disease by producing purposely alterations in structure and function under rigidly prescribed conditions.

HEREDITY AND DISEASE.

The mysteries of heredity have occupied the attention of the best minds from the earliest times to the present day, but we are almost as far from any adequate solution of them now as were the philosophers in the days of Lucretius. As concerns the process of fertilization, we have, it is true, gained much information that is interesting. There is good reason to believe that all higher organisms (including man) begin by the fusion of one male cell—the spermatozoon—with one female cell—the ovum. The single cell resulting from the fusion—the fertilized egg-cell—by multiple mitotic division gives rise ultimately to the billions of cells of which the fully developed organism is composed. Spermatozoa and ova are peculiar cells as regards the amount of chromatin which their nuclei contain. By the process of reduction-division (giving off of polar bodies) each ripe ovum comes to contain only half the number of chromosomes present in an ordinary cell of the body of the species concerned; in a somewhat different manner the testicular cells which give rise to the spermatozoa undergo a reduction-division by means of which each ripe spermatozoon contains within it also exactly half the number of chromosomes existent in the ordinary cells of the animal. When the male and female elements fuse, the resulting cell contains a number of chromosomes equal to that of the ordinary cells of the body. The centrosomes of the sperm-cell and the egg-cell fuse, and cell-division of the fertilized ovum begins, the mitosis being inaugurated by division of the newly formed centrosome, with assumption of polar position by the products of its subdivision. In each cell-division the chromosomes undergo longitudinal splitting, each into two hemichromosomes, each of which goes to form a chromosome of the daughter-cells; in this way each of the cells of the body appears of necessity to receive an equal share of the original maternal and paternal chromatin. There is a general belief, based on considerable evidence, that the function of the centrosomes is to determine the multiplication of the cells, while the function of the chromatin (composed of chromosomes) has to do with the production of form and the regulating of the activities of the parts, as, for example, in the differentiation into tissues and organs; to the protoplasm proper of the fertilized egg-cell is attributed the nutritive function, the capacity to attract and transform food-substances upon which depend the life and continued activity of the chromosomes and centrosomes. Interesting as is this belief,

it possesses no value at present other than that of an heuristic working hypothesis.

A description of the process of fertilization is no explanation of the essential nature of the phenomena of inheritance, nor does any one of the various theories which have been advanced—Spencer's doctrine of physiologic units, Darwin's theory of pangenesis, Haeckel's hypothesis of plastidules, or Weismann's germ-plasm theory—help us to any considerable extent toward an understanding of these phenomena. An enormous number of individual facts of the highest interest have been collected, but the generalization which will stand the test of all these is as yet lacking.

The question, Can the characters acquired during the lifetime of an individual be transmitted by that individual to his or her offspring? is one which is much disputed; there are able and enthusiastic supporters on both the positive and the negative side; it is safer for the student, at least in his earlier studies, to regard the question as still open. Pathologists, as a rule, have been forced by their observations to accept, as did Darwin and Lamarck, the positive view; while the majority, perhaps, of biologists have sided with Weismann in denying the possibility of the inheritance of acquired characters. It must be granted that much of what at first thought seems to be most striking evidence in favor of one of the views admits of ingenious explanation on the basis of the other theory.

In a discussion of hereditary disease a sharp distinction must be drawn between disease which is the result of abnormality of the fertilized egg-cell itself and disease which is the result of abnormalities in the environment of the egg-cell from the time of its fertilization up to the birth of the child. The latter should not be considered as inherited disease, but rather as environmental. The human organism begins with the fertilized egg-cell, and birth is only an incident in the life of that organism; in the sense in which we are considering it birth means only a change in environment—from a liquid medium of nearly constant temperature to a gaseous medium of variable temperature, and from a vascular food- and oxygen-supply to a condition in which for food and oxygen the digestive and respiratory apparatus of the organism are called upon to act. It is difficult to determine whether in a given instance a diseased condition is due to an inherited morbid state or to pathologic antenatal environment; but in any event it is helpful to have the distinction between the two sharply in mind.

So-called "variations" are particularly prone to be inherited, and in as far as these are marked deviations from the average they have to be looked upon as examples of pathologic inheritance.

One of the most interesting of the problems for physicians is that of the inheritance of infectious disease. That children are born sometimes with tuberculous, syphilitic, or streptococcic infection there can be no doubt; a large number of cases are on record; and as for tuberculosis, in the tissues of a certain number of newborn infants the tubercle-bacillus has been demonstrated either microscopically or by inoculation of susceptible animals. Certainly, the majority of those cases of infection met with in the newborn are not instances of *germinal infection* (or infection *ab ovo*), but are rather examples of *postgerminal antenatal infection*, the developing organism being infected by contagion from the mother. For in the first place it is doubtful whether a spermatozoon or an ovum containing tubercle-bacilli or streptococci would be capable of playing a successful part in the fertilization

process, and in the second place in a number of the instances encountered uterine or placental disease of the mother has been demonstrated. That germinal infection can occur in animals has been proved in at least one instance—that of *pébrine*, the disease from which silkworms suffer. Without going into the evidence, it may be said that it seems most probable that congenital syphilis is, in some instances at least, a matter of germinal infection in human beings; though doubtless many or most of the cases of congenital syphilis are to be regarded as examples of postgerminal antenatal infection as a result of intra-uterine contagion. The evidence—observation as well as experimental—available at the time of writing is all against the view that tuberculosis or pyogenic infections are ever germinal in origin.

Hemophilia, the condition which exists in the families of “bleeders,” appears to be a disease which more than any other supports the doctrine that pathologic conditions can be inherited. There are on record very complete genealogic trees which prove that hemophilia is transmitted for many generations. Males are much more frequently affected than females; but females who are not bleeders, but who have had bleeding ancestors, may transmit the disease to their male offspring. So little is known of the exact nature of the disease that it is not possible to decide at present whether it represents a “variation” or an “acquired” morbid condition which becomes hereditary.

Diabetes insipidus is another disease which may affect several generations in succession. Males and females appear to be about equally affected.

Deaf-mutism presents interesting features from the view-point of heredity. Congenital deaf-mutism has to be distinguished from deaf-mutism resulting from disease in infancy. Marriages between deaf-mutes result in a high percentage of deaf-mute offspring, but marriages between deaf-mutes and hearing persons result in a still higher percentage of deaf-mute offspring. The explanation appears to be that of the marriages of deaf-mutes with one another, many of the participants are not hereditary deaf-mutes, while in marriages of deaf-mutes with hearing persons the latter are most frequently drawn from families in which hereditary deaf-mutism occurs, and, though not deaf-mutes themselves, possess germ-cells which transmit the affection.

Certain vices of metabolism, such as gout and chronic rheumatism, undoubtedly run in families, and are classed as hereditary diseases. The external manifestations of a gouty condition may vary considerably, even in the offspring of the same individual; thus, while one of the children may, like his father, develop typical gouty joint-affections (*homeomorphous inheritance*), another may be an asthmatic, and still another, perhaps, a sufferer from migraine (*heteromorphous inheritance*). Among the most striking examples of this dissimilar, or so-called heteromorphous, inheritance are those met with in the domain of neuropathology. It is far less common to find children inheriting the same disease as that occurring in one or both of their ancestors than to meet with those who suffer from some nervous disease other than that by which their ancestors were attacked. By many it is believed that only a “neuropathic predisposition” is inherited, and that the character of the nervous disease which develops is dependent upon the particular form which this predisposition takes, together with the special noxæ to which the individual during his lifetime is exposed or from which he is protected. A remarkable attempt to illustrate such heteromorphous heredity

in fiction has been made by Emile Zola in his series of novels dealing with the Rougon-Macquart family.

The so-called homeomorphous heredity is well illustrated by the "family diseases" of the nervous system, such as Friedreich's ataxia, and some forms of insanity.

An hereditary tendency to the formation of neoplasms has been emphasized by many authors; the view agrees well with the theory of the origin of tumors advanced by Cohnheim, but a careful analysis of available statistics does not warrant the conclusion that new growths are inherited.

Ehrlich's experiments with abrin, ricin, and other poisons indicate that immunity from intoxication can be transmitted from mother to offspring, and observations on some of the infectious diseases make it probable that a temporary and probably passive immunity can be given to the offspring in such cases by the mother. There is no evidence that an immune father can confer immunity upon his descendants. It seems likely, therefore, that the immunity given by the mother is not a germinal immunity, but a chemical and passive immunity yielded through the maternal blood-supply. In other words, we have at present no evidence of direct inheritance of acquired immunity, but rather some instances of temporary immunity conferred by postgerminal antenatal environment. It is different with natural immunity. This is undoubtedly a matter of inheritance, but in all probability not an example of inheritance of acquired immunity. It would seem much more likely that through natural selection the specially insusceptible had survived, the susceptible sometimes dying from the disease and yielding a less numerous posterity, gradually becoming eliminated.

Some infectious diseases of the parents, instead of making the offspring less susceptible than other individuals, have the opposite effect. This is pre-eminently true of tuberculosis; but just how tuberculosis of the parent gives rise in the offspring to an *hereditary predisposition* to tuberculous infection remains for the present obscure.

That the future has much in store for us in the clearing up of the problems of pathologic inheritance no one can doubt. A valuable clue and a basis for experimentation lie in the important fact that the ovaries and testicles are nourished by the blood of the general circulation. That the nutrition of these organs must vary with alterations in the general nutrition of the body seems obvious; that the cells of these organs can escape the ill effects arising from the action of poisons in solution in the general circulating blood would seem impossible. In thus far, at any rate, the acts of the parents cannot fail to influence their offspring either for good or ill, and the advice of Jean Labor, in his Benediction of the Persian Marriage, aptly cited by Le Gendre, cannot be too often repeated:

"Pour que vos actions ne soient vaines ni folles,
Craignez déjà les yeux futures de vos enfants."

ENVIRONMENT AND DISEASE.

Living organisms, multicellular as well as unicellular, at all stages of their existence are exposed to influences acting upon them from without. Indeed, in the absence of these influences life is scarcely conceivable, for the phenomena of life with which we are familiar appear to consist exclusively of a continuous adjustment of internal to external relations. There is no

evidence whatever of spontaneity of action in any living organism ; on the contrary, all known facts favor the view that every manifestation of energy on the part of an organism is to be looked upon as a reaction to some external influence. The reaction to external agents is not always immediate, however ; the cells of the body have the capacity of storing up stimuli, as it were, until through a process of summation some final stimulus leads to a discharge. This accounts for the fact that a vital reaction often appears to be out of all proportion to the external influence immediately occasioning it, when in reality this influence is only the last of a series of stimuli which at various times during the life of the organism have acted upon the cell or group of cells representing the physical basis which underlies the reaction. It is in connection with the nervous system especially that such retarded reactions are very commonly noticed.

The environment to which every human being is exposed varies enormously at different periods of life ; the most abrupt change is that which occurs at his birth, but throughout later life there are continual slight alterations, and, with the majority of individuals, frequently changes of a very decided character. With a given inheritance, the individual which results can vary only according to the environmental influences which act upon the organism from its beginning as a fertilized ovum to its death.

It is convenient to divide environmental influences chronologically into (1) those which act before birth and (2) those which affect the individual after his birth ; or, briefly, into *antenatal* and *postnatal environment*.

Although the period of antenatal environment is very short as compared with the average duration of postnatal influences, it is of the very highest importance as regards the future welfare of the organism concerned. This antenatal period is arbitrarily divisible into an *embryonal period* and a *fetal period* ; the former corresponds in human beings to about the first two months of gestation, the latter to the remainder of intra-uterine existence. During the embryonal period the fertilized egg-cell rapidly divides, differentiation of cells takes place, and the organs of the body are formed ; during the fetal period the organs thus formed increase in size and begin to take on their characteristic functions. In both stages of this antenatal period the organism is dependent upon influences outside itself—on gravity, warmth, an adequate amount of food-supply of the right sort, etc. Considerable deviations from a certain normal standard of these external influences can and do lead to pathologic conditions in the developing organism. In the embryonal period especially abnormal environmental relations may lead to the most serious results ; for since this is the time when the various organs are being formed, there may be arrest of development, excess of development of certain parts, or a perversion of the organ-formation ; accordingly, this is the period when the fate of the form of the organism is decided, whether the normal form of the species will be attained or whether a malformation or a monster will result. The experimental teratologists have furnished us with valuable data as to the effects of abnormal environment of various sorts, and monsters of different kinds can be produced by submitting the fertilized egg-cell, the segmentation-cells, or the blastoderm to the effects of light, cold, heat, variations in oxygen-supply, and especially certain chemical agents. That morbid form-relations in the organism can be dependent upon abnormal environment in the embryonal period may, therefore, be considered as proved, and pathologists are busy studying the

various abnormalities which may occur in human beings as a result of injury at this time, and are endeavoring—though as yet with but little success—to determine the exact relations which exist between a given alteration of the environment and definite anomalies of development. The difficulties of the study are obvious, and are not lessened by the fact that one primary developmental alteration may carry in its train as sequences a whole series of secondary alterations in the embryo.

Though not proved, it is *a priori* extremely probable that poisons acting electively on the embryo at an early period of cell-differentiation can render permanently abnormal one or more cell-systems of the body; it is not impossible that one day an explanation of the low resistance offered by certain of the tissues of some individuals in adult life may here be found.

In the fetal period of antenatal environment the organism is endangered less by the effects of physical agents than by those of a chemical nature. The chemical constitution of the maternal blood is of prime importance at this stage. Infections, and more particularly intoxications, of the mother may be transferred to the child; uterine or placental diseases especially may be of very serious import for the fetus. Children born with tuberculosis, syphilis, or pyogenic infections are nearly all instances of contagion from antenatal environment. At the time of birth itself a narrow pelvis in the mother or the use of forceps by the physician may mechanically injure susceptible parts—especially the head—of the child. Considering all the avenues of danger open, it is surprising that so many children are born healthy; it is fortunate, too, that, thanks to the seething energy of the developing cells, the reparative and adaptive powers are at a maximum in these early stages of life.

Postnatal environment beginning at birth continues throughout the remainder of the life of the individual. The external influences which can act upon man are, in the last analysis, either chemical or physical; the medium in which he lives, the air he breathes, the food-stuffs taken, the temperature of his surroundings, gravity, light, electricity, and ether-waves are among the things to be considered. The external agencies which act through the sense-organs—the ether-waves that affect the rods and cones of the retina, the air-waves that set in motion the vibratory apparatus of the ears, the chemical substances which act upon the olfactory and gustatory mucous membranes, the mechanic and physical agents which start the impulses in cutaneous sensation—belong to the same category. In conscious life memories are called forth and association processes are started into activity by stimulation of one or more of the sense-organs by these physical or chemical environmental influences; even the influence of one mind upon another is possible, as far as we know, only through the sense-organs of the one influenced.

With a given inheritance the best development of the capacities of an organism doubtless requires a specific environment varying constantly according to the needs of infancy, adolescence, and the stages of adult life. But our knowledge of the relations of specific environments to definite inheritances is so extremely limited that few would be rash enough to have much faith in their prescriptions in a given case. Moreover, aside from the impossibility of knowing what a given inheritance is, there is seldom opportunity for more than meager alteration of environment by prescription; in most particulars this is predetermined, a given human organism living of

necessity in a particular region with its geologic formation and meteorologic influences, subject to the racial conditions in which he is born, surrounded by the conditions pertaining to the social level in which he happens to be placed and to the special modifications of these which the occupation of his parents and his own, in the general division of labor, necessarily entails. Of the vast number of potential capacities inherent in each developing individual, the one which shall be especially developed at the expense of the others is decided by certain exigencies in environmental relation—sometimes by such as we are accustomed to designate as “merely accidental.” The result is, therefore, that the environment which comes to a given inheritance is very far removed from that which an all-seeing intelligence would prescribe as that specifically ideal for the individual. No individual finds a perfect environment; but the degree of dissonance varies enormously in different cases, and though the wonderful adaptive powers of an organism permit it in many instances to attain to a comfortable and profitable state of existence, in an appalling number of cases the lack of harmony is so great that a high degree of discomfort and inefficiency, disease, or premature death is the outcome. It may be true that for the good of the species, or for the welfare of living organisms as a whole, such a state of things is desirable; indeed, this is in large part the basis of the doctrine of evolution, with its tenets of “natural selection” and “survival of the fittest.” A favorable environment in any case is not one free from struggle, but rather one in which the organism is victorious in its conflicts and in which the victory is not bought at too great a price.

All pathologists are now agreed that by far the majority of pathologic conditions are the result of external causes; *i. e.*, are due to inimical environmental influences. These are divisible into (1) *efficient causes* and (2) *predisposing and accessory causes* of disease.

The *efficient causes* of disease (*causæ proximæ sive determinantes*) are the immediate or direct causes. Thus, the cholera-spirillum is the efficient cause of cholera, the *Micrococcus lanceolatus* is the efficient cause of acute lobar pneumonia, the heat of the sun's rays of insolation, lead-poisoning of wrist-drop.

The *predisposing and accessory causes* of disease (*causæ predisponentes sive remotæ*) include those which render the body more susceptible to the efficient cause. Thus, external agents which render the contents of the stomach alkaline are believed to predispose to infection with the comma-bacillus of cholera; exposure to cold and wet predisposes to acute lobar pneumonia; alcoholism predisposes to insolation; and certain occupations make lead-poisoning possible, and in a sense may therefore be regarded as remote causes of lead-paralysis. That an efficient cause of one disease may be a predisposing cause of another disease, and *vice versa*, is obvious.

In the special sections of this work the various diseases together with their immediate and remote causes will be discussed. The influence of mechanic injury, of physical agents—heat and cold, light, electricity, *x*-rays—and especially of chemical agents, including the various poisons, will be considered; especial attention will be paid to bacterial infections and invasions by animal parasites, conditions in which poisoning is the chief factor, as a rule, though mechanic injury plays sometimes also a part; reference will be made in some instances to the pathologic reactions called forth by way of the nervous system, a most important field for study,

but one which is as yet only being approached. An attempt will be made also to pass beyond the mere etiology of the various diseases, and, where knowledge warrants it, to enter into a description of the pathogenesis of the different processes, for even more important than to know *why* disease occurs is to know *how* it originates.

HEALING AND CURE.

When the external influences acting upon the cells of the organism are so pronouncedly inimical that certain of those necessary for the continuance of life are so injured as no longer to be capable of performing their functions, death occurs. Until death occurs, or in case it does not occur, the organism attempts to protect itself against injury, to repair the injury done; or, in case the injury is irreparable, to adapt itself as well as possible to the altered conditions under which it has henceforward to live. These efforts constitute what is ordinarily designated as the "healing power of nature" (*vis medicatrix nature*). In general parlance the word *healing* is applied most often when surgical injury is in mind, the word *cure* when internal pathologic processes are thought of; but the distinction is merely arbitrary, and the two words are frequently used indiscriminately. The protective, antidotal, regenerative, compensatory, and adaptive capacities of organisms are among the most interesting subjects with which the pathologist has to deal, and it is chiefly from a study of them that methods of successfully dealing with the natural processes spring. Natural attempts are sometimes excessive and need to be limited; at other times they are defective and require to be supplemented; here lies the province of *therapy*.

In the process of evolution special mechanisms capable of protecting organisms against injury from the external agents ordinarily encountered have been developed; but these, wonderfully intricate and ingenious as many of them are, are frequently insufficient; the organism has then to combat as best it can the effects of the injury. The struggle of the human organism against bacterial infection may be taken as an example. The environment of each individual is such that he comes into contact relation with certain microorganisms which are capable of causing disease in human beings. He is constantly in contact with some of these, only occasionally in contact with others. His protective mechanisms, if in normal condition, protect against the ingress of most of these microorganisms; there are some against whose ingress there seems to be no normal protective mechanism. If from any cause there is a breach in one of the natural barriers, bacteria against which there is normally protection may enter the organism, multiply, and by their toxic products injure the cells of the body. Efforts are made to kill the invading organisms (*phagocytic activity of the cells, bactericidal power of the blood and tissue-juices*), to wall them off (*inflammatory reaction, encapsulation*), to get rid of their toxic products (*increased activity of eliminative organs*), or to neutralize their effects (*development of antitoxins*). If the infection leads to the death of some of the cells, they are replaced by cells of the same kind (*regeneration of tissue*); or if this, owing to the extent of the injury or the nature of the tissue injured, is impossible, by cells and intercellular substances of a different kind (*proliferation of connective tissue or glia, cyst-formation*). Some of the injuries caused to certain organs may never be directly reparable; then often secondary alterations in other and

often distant organs are necessary to reëstablish the vital equilibrium (*compensatory and adaptive processes*). Not infrequently an infection leads to the development in the organism of entirely new mechanisms of defence which protect it from any subsequent infection of the same kind (*acquired immunity*).

It is seldom that what we designate as healing or cure is associated with a complete restoration of the previous condition (*restitutio ad integrum*); indeed, it is likely that every disease-process leaves behind it indelible alterations in some of the cellular constituents of the body. These cellular bequests may be of little or no significance at times; in many cases, however, they are responsible for the development later in life of pathologic processes of a serious nature.

IMMUNITY.

When an organism, subjected to the action of some influence noxious to certain other organisms, is found to be insusceptible to it, that organism is said to be *immune* from that particular noxa. If this immunity has been enjoyed by the organism from its beginning, and has not been due to reactions occurring in it during its lifetime, the immunity is said to be *natural, innate, or hereditary*. If, on the other hand, the immunity is the result of changes which have taken place in the body during the lifetime of the organism, it is spoken of as *acquired immunity*. Immunity gained during the intra-uterine life of a higher animal may be called *antenatal acquired immunity*, while that developed during its subsequent life may be referred to as *postnatal acquired immunity*. Immunity is usually acquired by an organism after an attack upon it by some external agent, coming to it accidentally in the course of its life. This may well be designated *unintentional immunity*. It can be acquired in a certain number of instances through the direct, purposeful intervention of human agency, in which case we may speak of *intentional or artificial immunity*.

Though in the strict sense of the word immunity indicates complete protection, it is not customary so to limit its meaning. Complete insusceptibility is referred to as *absolute immunity*, while lesser degrees of insusceptibility, a certain marked resistance to injury being offered, are spoken of as *relative immunity*.

Natural, Innate, or Hereditary Immunity.—It has been known for ages that certain organisms are naturally susceptible, while others are naturally resistant to given noxæ. Species and races show marked differences in this regard. Many species of animals are seriously poisoned by the venom of the viper, while the hedge-hog is naturally immune therefrom. Man is susceptible to many infectious diseases—*e. g.*, typhoid fever, syphilis—which, as far as we know, never occur in the ordinary course of nature in other species of animals. Again, various infections to which animals are very susceptible may not influence human beings, or only to a limited extent. Different races of men vary much in their susceptibility to poisons and infectious agents. The negro has a relative immunity from the effects of alcohol; he is but seldom attacked by malaria or by yellow fever.

With a given species, natural immunity varies with the age of its constituent individuals. Thus, for example, typhoid fever is rare in human beings in infancy. Children possess a relative immunity from the effects of arsenic, belladonna, and other poisons. It is uncommon to meet with cases of osteomyelitis in adults, while the disease is frequent in the young.

Again, among individuals, even when of the same age, there are remarkable variations in susceptibility to noxæ. Thus, most people can take relatively large doses of quinin without suffering inconvenience; others are cinchonized by small doses of the drug. In epidemics of cholera, small-pox, yellow fever, bubonic plague, etc., there are certain individuals who, never having had a previous attack and in spite of manifold opportunities for contagion, never contract the disease.

Most interesting are the differences in resistance offered by the various organs and tissues of the same individual in cases of intoxication or infection. The pathologist is constantly struck by the relative immunity of certain organs—*e. g.*, in tuberculosis, in typhoid fever, in pyemia.

Acquired Immunity.—The tolerance acquired to poisons by those who begin with small doses and continue their use, gradually increasing the amount taken, is matter of common experience. The alcoholic *habitué*, the morphinist, the Styrian arsenic-eater, will be immediately recalled to mind.

Many infectious diseases yield immunity by a single attack. Scarlet fever, small-pox, typhoid fever, syphilis, seldom affect an individual more than once, and when they do the second attack is always extremely mild. Here we have to deal with postnatal unintentional acquired immunity.

Children born of a mother who has suffered from small-pox during her pregnancy and recovered without miscarriage may be (but are not always) immune from small-pox—an example of antenatal acquired immunity.

The history of artificial acquired immunity begins with the introduction of vaccination by Jenner. With the advent of the bacteriologic era and the establishment of the relation between definite bacteria and specific infectious diseases, Pasteur and his co-workers attempted to produce artificial immunity against bacterial infection. He was able by inoculation of chicken-cholera bacilli whose virulence had been artificially attenuated to protect animals against infection with virus of full strength. It was soon found possible to produce immunity against a whole series of infectious diseases by inoculation of weakened cultures of bacteria or by ingestion of their products. Protection against anthrax, rabies, bubonic plague, and cholera can be afforded to human beings in this way. These immunizing methods were, however, all preventive rather than curative.

A method which will cure an infection already in progress has been found for a certain number of diseases, the most striking example of which is diphtheria. The blood-serum or other fluids of an animal rendered artificially immune from diphtheria, when injected into an animal suffering from the infection, will afford speedy relief. The healing substances in the serum of the immunized animal—so-called antitoxins—can be enormously increased in amount by special methods. Antitoxic serums against diphtheria, tetanus, and snake-poison have been made practically useful; the results in diphtheria are eminently satisfactory, but in tetanus there is still much to be desired. This rapid form of vaccination can also be employed as a prophylactic measure, but it yields only temporary immunity. It has been called *passive* immunity by Ehrlich, to distinguish it from the *active* immunity yielded by an actual attack of the disease or by vaccination with the bacteria or their toxic products.

Theories of Immunity.—A number of theories attempting an explanation of the essential nature of immunity have been advanced. Of those supported at the moment, two main groups may be distinguished:

1. The *humoral theories*, which attribute immunity to the properties of the extracellular fluids of the body (bactericidal, attenuating, antitoxic properties); and 2. The *cellular theories*, which assume that the body is protected through the direct and active intervention of the living cells themselves.

The **humoral theories** are based largely upon the studies of Fodor, Nuttall, Flügge, Behring, and Buchner. They assume that the bacteria are killed through the bactericidal action of the blood-serum itself, or that the poisons produced by the bacteria are rendered inactive, according to Buchner, in that the blood-serum renders the specifically irritable cells of the body insusceptible to the action of the poisons, or according to Behring, in that the blood-serum actually destroys the poison made by the bacteria. The bactericidal power of the blood is attributed by Buchner to the presence in it of certain labile chemical bodies, which he calls *alexins*, and to which Hankin has given the name *defensive proteids*; these bodies are believed by Kossel and by Vaughan to be derived from nuclein or nucleinic acid. Baumgarten questions the presence of specific bactericidal substances in the serum, and believes that its action can be explained on the grounds of plasmolysis. If this be so, it is strange that the bactericidal power should be abolished by heating to a temperature of from 57° to 60° C. That no change in the ionic concentration of the blood-serum demonstrable by the methods of measuring electric conductivity results from this heating, has been proved by Looitz and Tallant. Even those who adopt a humoral theory of immunity grant that the bactericidal, attenuating, and antitoxic substances are derived from the cells.

Metschnikoff's **phagocytic theory** of immunity is the chief of the cellular theories. The learned biologist at the Pasteur Institute has during the past sixteen years combated, he believes successfully, every objection which has been raised against his doctrine. Immunity, he asserts, is dependent upon the activity of the living cells. Any bactericidal action of the body-juices is the result of secretions derived from stimulated leukocytes or endothelial cells. Among the cellular elements which take part in immunity, the phagocytes occupy the first rank. The main factors of the activity of the phagocytes are their sensibility and motility, their capacity of taking up solid bodies, their power of forming substances which will kill and digest microbes. If these properties are possessed in such a degree that a given pathogenic microbe cannot develop in its body, an animal is said to be naturally immune against that microbe. If all or one of these capacities should be insufficiently developed, the animal is susceptible. If the microbial products call forth a negative sensibility in the phagocytes (negative chemotaxis), as in the acute septicemias, then the parasites increase, as in a culture-tube, and soon kill the organism. Should the products of the microbes positively influence the phagocytes so that the latter become directed toward the microbes, but are unable to ingest them, the animal cannot live (*e. g.*, anthrax infection of the guinea-pig). In an infection in which the phagocytes are attracted by the microbes and the latter are ingested by the former, if the cells are not able to kill the microbes within their bodies, the course of the infection is slowed more or less, but death ultimately results (*e. g.*, mouse-septicemia, tuberculosis in susceptible animals).

The activity of the phagocytes is, Metschnikoff continues, artificially alterable. Thus fowls, ordinarily immune from anthrax, can be rendered artificially susceptible by exposure to cold. Further, an animal ordinarily

susceptible to a given infection, can through stimulation of the phagocytic activity be rendered artificially immune. If this stimulation be temporary (as in the passive immunity of Ehrlich), then the immunity lasts but a short time; if it be produced by inoculation of the bacteria or their products (as in the active immunity of Ehrlich), it may last for a much longer period.

A full discussion of the subject of immunity cannot be entered into here. It may suffice to say that with this subject, as with so many which are energetically discussed, the truth appears to lie in a mean which harmonizes more or less the two opposing views. Both the cells and the extracellular fluids are concerned in the phenomena of immunity, each probably varying in degree in the different varieties of the process. Immunity is a most complex subject, and a satisfactory explanation for one infectious disease will by no means hold for another.

A word must be said with regard to the **lateral chain theory** (*Seitenkettentheorie*) of Ehrlich. This ingenious experimenter works on the hypothesis that in the protoplasm of the body-cells are contained highly complex organic molecules with a tolerably stable central group, to which are attached far less stable lateral chains of atoms or atomic groups—lateral chains (*Seitenketten*). The ordinary chemical transformations in the protoplasm are carried on by means of these lateral chains, the stable center of the molecule remaining unaffected. Poisons entering the body do injury if they find lateral chains with which they can unite (*receptors*); as lateral chains become united with these poisons the cells are stimulated to form new lateral chains, and, according to a well-known physiologic law of regeneration, will build them in excess. Ehrlich assumes in an animal rendered artificially immune from diphtheria that there is an overproduction of lateral chains by the cells, and it is these excessive lateral chains which, thrown off by the cells into the blood, constitute the antitoxins. These free lateral chains of antitoxic serum can bind and so render neutral the toxins produced by the diphtheria-bacilli, thus preventing their union with the lateral chains of the body-cells themselves. Ehrlich's explanation of immunity in infectious diseases like typhoid fever, cholera, and the like is somewhat similar. Immunity in these cases is antibacterial rather than antitoxic; that is to say, the body-fluids of immune animals destroy the typhoid bacilli and the cholera-bacilli themselves, instead of rendering neutral their poisons. In this form of immunity the lateral chains produced in excess by the body-cells act as the *immunizing body*, but in a peculiar way. In the normal blood-serum are contained substances which possess the power of dissolving bacteria, but these substances cannot act except by the intervention of another chemical substance. This intermediate rôle is played by the immunizing body. Only after the latter has united with the protoplasm of the bacterial cell can the dissolving substance (*addiment, end-body, or complement* of Ehrlich) unite with it and begin its solvent effect. Ehrlich and Wassermann believe that by regulating the amounts of the *immunizing body* and the *complement* in curative serums it may be possible to make serotherapy practically useful in a group of diseases in which it has hitherto been of no avail.

Immunity can be produced not only against poisons and bacteria, but also against a variety of animal cells, such as spermatozoa and red and white blood-corpuscles. In the production of these immunities a variety of cell-destroying substances (*lysins* of Ehrlich) are formed. These in turn, if introduced into the body of another animal, may give rise to *antilynsins*.

Autolysins, homolysins or isolysins, and heterolysins are distinguished according as the lysin produced destroys cells of the animal's own body, those of an animal of the same species, or those of an animal of a different species; but the subject grows too complex to be further followed here.

ADAPTATION IN PATHOLOGIC PROCESSES.

In pathology the term adaptation is employed to designate the morbid processes—compensatory, regenerative, self-regulatory, protective, or healing—which bring about some sort of adjustment to changed conditions due to injury or disease.¹ Adaptive processes in physiology are familiar to all; the maintenance of an almost constant temperature in higher animals notwithstanding marked alterations in the temperature of the environment, and variations in the amount of heat produced in the body itself, and the regulation of the force and frequency of the beat of the heart according to the amount of work it has to do, are striking examples.

Physiologic adaptations must be looked upon as cellular responses to environmental alterations dependent upon innate properties in the cells, which in turn, in large part at least, are dependent upon evolutionary factors. It does not seem likely, however, that variation, natural selection, and heredity can have operated directly so as to endow the cells of an organism with properties which especially fit them to meet pathologic emergencies. On the contrary, the evidence is in favor of the view that all or nearly all adaptations under pathologic conditions have their foundation in physiologic processes or mechanisms (Welch). As examples of adaptation in pathologic processes may be mentioned the cardiac hypertrophy which accompanies chronic renal disease, the compensatory hypertrophy of the heart when there are serious lesions of one or more valves of that organ, the collateral circulation which develops when there is obstruction to the flow of blood through the portal vein, the vicarious emphysema of one part of a lung when another part of it is consolidated, the increase in size of cells and their multiplication in one kidney when the other is diseased or has been removed by the knife of the surgeon, the thickening in the wall of a blood-vessel which occurs when the tension inside that vessel has for a long time been increased, the reorganization of the functional activity of neural complexes when one or more neurone-systems have been thrown out of function. The various pathologic regenerations, and even inflammation and acquired immunity, may also with fairness be included under the head of adaptive processes which follow injury or disease.

The inadequacy of pathologic adaptations contrasts markedly with the perfect compensations afforded by physiologic adjustments. While the purposefulness and benefit of the adaptive changes in many pathologic processes are obvious, their inefficiency and even dangerous consequences are only too frequently observable. The thickening of the vessel-wall in arteriosclerosis has its advantages, but it is far from being a satisfactory adaptive arrangement. The reaction of the body-cells to the syphilitic virus is doubtless protective in nature; but when a gumma presses upon an important convolution in the brain the benefit is more than counterbalanced by the attendant

¹ For a more extensive discussion of this subject, the student should consult the article by W. H. Welch, "Adaptation in Pathologic Processes," Congress of American Physicians, iv., 1897, *Science*, N. S., vol. v., No. 126, pp. 813-832, 1897.

evil. The benefit or harmfulness of the adaptive processes has been much discussed in connection with inflammation. Some view inflammatory processes as almost always inimical to the organism, always to be artificially combated; others regard them as the best protective mechanisms which the organism under certain conditions possesses, mechanisms which are to be controlled and aided artificially rather than combated. One thing we may be sure of, the phenomena of inflammation, like those of all other processes, are the necessary sequence of the interaction of external forces and the forces inherent in the cells themselves.

Given an organism made up of cells with certain innate properties, the response to stimuli from the outside will vary with the external stimulus, but will always be determined by the nature of the substances and forces inherent in the cells. It is the function of the pathologist to discern as best he can the mechanic factors which underlie adaptive responses; in this task he is more likely to be hindered than to be helped by indulgence in teleologic considerations. Were the adaptations in what we call pathologic processes perfect, there would be no need of therapeutic interference; as it is, however, their imperfections stimulate the physician and surgeon to ever-renewed exertions.

ON THE METHODS OF STUDYING PATHOLOGY.

The phenomena of disease are so complex and the problems connected therewith so difficult that it is folly for the untrained mind to approach them. Before entrance upon the study of pathology, therefore, a liberal education is a *sine quâ non*. There is difference of opinion regarding the most desirable extent of this preliminary training, but most will agree that it should go far enough to put the student on a level with the liberally educated men of the professions of law and theology; and that it should not be prolonged to an age when plasticity is endangered, for the student should enter upon the study of pathology while he is still easily impressionable and capable of an ardent enthusiasm.

In his early education the subject-matter of the student's work is probably less important than the manner of it; with whatever his studies may be concerned, the essence of the training should be directed toward the development of his powers of analysis, the cultivation of his imaginative faculties, the strengthening of his capacity for weighing evidence, and, above all, the encouragement of the expressive activities. The mind trained to observe accurately and to think logically, if combined with imaginative powers, will be the one most likely not only to grasp quickly knowledge already existent, but also to add to that knowledge.

Since disease represents a deviation from the normal, it goes without saying that its processes must remain unintelligible to one unacquainted with normal structure and function. Just as physics and chemistry are subjects, the study of which necessarily precedes a successful study of anatomy and physiology, so the study of the latter subjects naturally antedates the study of pathology. Again, comparative anatomy and physiology, along with embryology, have thrown much light upon the structure and function of the normal human organism; they are also very useful in helping to explain many of the phenomena met with in diseased conditions—indeed, we owe no small part of our modern conceptions in pathology to phylo-

genetic and ontogenetic considerations. A study of these subjects, therefore, will naturally be prefatory to a study of pathology.

It is by no means necessary that the student of pathology shall be equally well prepared in all these antecedent studies—biology, physics, chemistry, anatomy, physiology; on the contrary, with a good general knowledge of each he may be the better able to make advances in pathology if he have had a very special training in some one of them—witness the value of Pasteur's knowledge of chemistry, of Helmholtz's command of physics!

To keep pace with the world's activities in the domain of pathology the student has to follow closely the books and periodicals bearing upon the subjects which are constantly appearing. To do so he has at present to read several languages in addition to English. French and German are essential; and Italian is desirable; Spanish and Russian are of less service, though occasionally of advantage.

Diseases or their effects may be studied in man and animals during life or after their death. The studies made during the life of human beings are usually spoken of as *clinical*; those made after death upon human beings and those made both before and after death upon animals are usually carried on in the *laboratory*. No sharp line can, however, be drawn between clinical and laboratory studies; the laboratory is only an extension of the hospital ward, and in a sense the ward may be regarded as a form of laboratory; in both places pathology, the study of disease, is the subject prosecuted.

In the solving of problems in pathology both inductive and deductive methods are employed, for sometimes the latter are applicable when the former offer no satisfactory modes of approach. When investigating pathologic processes in human beings we are limited almost entirely to observational methods; but in animals, fortunately, the results of observation may be supplemented by those of experimental inquiry. All scientific work is based upon the assumption that the course of nature is constant; in other words, that the world of phenomena is reducible to a series of uniformities which are designated ordinarily Laws of Nature. In the study of the phenomena of disease we have to attempt to reduce the more complex uniformities met with to terms of the simpler uniformities of which they are composed. The relations of a given phenomenon to those which coexist with it, to those which have preceded it, and to those which will follow it, have to be determined. Here the powers of *observation* have to be strenuously exerted. At any given moment in the course of a given disease a complex group of phenomena presents itself for examination. This group must be analyzed; the observer strives to make out the individual parts of which the whole complex is composed. All the phenomena observable have to be regarded as consequents of antecedent phenomena. The inquiry has then to be directed toward the antecedent phenomena, and the attempt made to determine which consequents are related to which antecedents; antecedents and consequents are in every instance observed so numerous that in order to establish any relations of cause and effect it is necessary to observe other instances in which some of the antecedents are present, separated from the rest, and see what is the result of them; or to study other instances in which some only of the consequents present themselves, and find out which of the former antecedents existed and which were absent. In this way only is it possible to determine the *unconditional antecedent* or *cause* of a given consequent.

In order to "vary the circumstances" with this purpose in view, we must "interrogate Nature;" we may either wait until Nature in her ordinary course provides us with a suitable instance for observation, or we may contrive to produce the instance artificially—in other words, resort to *experiment*.

The pathologist who works with living human beings—be it in the hospital ward or in private practice—is dependent, as has been said, mainly upon his powers of observation. Some experiments he can perform, but these must be harmless and painless; and, as a rule, they have to be limited to procedures which will help to clear up the diagnosis and to measures which it is believed will be of therapeutic value.

The pathologist who works in the laboratory can supplement the results of observation by resorting to experimentation. His study of the human body is, it is true, confined to the examination of dead tissues or to the investigation of fluids or solids removed from the living; with animals, however, he is not so limited, but can study both the living and the dead, varying the circumstances at will.

It is of the utmost importance that the study of clinical pathology and that of laboratory pathology be intimately associated. Though through the division of labor it has become necessary that a man devote himself mainly to one or the other, still to be successful as a clinician much help is gained by prolonged experience in the methods of the laboratory, while to study pathology experimentally with hope of satisfactory results extensive preliminary clinical observations are highly desirable. If the two sides are divorced, there is an end of progress.

The clinician can only to a limited extent control his material; he has to observe the cases of diseases as Nature provides them to him; he cannot have a case presenting given phenomena at any moment he wants it, but, ever on the alert, must grasp as best he can the passing picture, preserving it as well as is possible in a clinical record. The experimental pathologist, when he has once established a definite relation of cause and effect with a given phenomenon, can reproduce that phenomenon at will and study it repeatedly by itself, or, by combining the causal antecedent with a variety of other antecedents, he can watch the modifications in consequents which result. He has, it is true, always to make his experiments from antecedent to consequent; he cannot directly experiment from consequent to antecedent. The starting-point of an experimental inquiry is nearly always an observation, but this need not always be so; on the contrary, experiments may be undertaken to test the validity of a theory or hypothesis.

How should one approach the study, then, of pathology? Observation should certainly precede experiment. It seems desirable, too, that there should be a certain sequence in the subjects of observation. Thus, in the wards the study of external pathology (clinical surgery) should precede the more difficult study of internal pathology (clinical medicine), and in the laboratory the pathology of the organs (gross pathology) should precede the pathology of the tissues and cells (pathologic histology). After a certain amount of empiric knowledge has been gained it is time to begin the interrogation of Nature—to trace the relations of antecedents and consequents, of cause and effect (pathogenesis and etiology). Here observation is still helpful, but experiment becomes infinitely more valuable. The complex phenomena of individual disease are gradually decomposed into

their simplest elements (special pathology), after which various diseases can be compared with one another, and, generalizing from multiple experiences, laws which hold for pathologic processes in general can be formulated, and the relation of them to the simplest laws of Nature can be established (general pathology).

While the above in general would seem to be the natural sequence of study and investigation, most find that they do well to make a circle of the sequence, traversing this circle at least several times. On each journey new view-points are attainable by virtue of previous experiences. Once well acquainted with the principal phenomena all around, residence for a prolonged period on some one part of the circle can more safely be indulged in.

The work which a pathologist accomplishes is dependent upon the quality of his mind and the opportunities available to him. All pathologists worthy of the name undertake original investigations. Only a few make great discoveries, but it is vouchsafed to many to make minor contributions to knowledge. The greatest minds devise new methods of work, new ways of approaching problems; lesser intelligences travel along the paths which genius has indicated, and make discoveries by applying the methods which genius has invented. Great minds provide the new ideas; lesser minds confirm them.

The beginner does well to associate himself with a master. A master will help him with rules for observing and with methods of interrogating Nature by observation and experiment. He will encourage him when in difficulty, and will hold him in check when he tends to a tangential course. Above all, by his example, he will afford him the greatest of all stimuli, that which lies in the demonstration that valuable results come only through patient, long-continued, rigorously controlled work.

GENERAL MORBID PROCESSES.

DISTURBANCES OF THE CIRCULATION.

Introduction.—The heart-muscle is an apparatus which transforms the chemical energy brought to it by the blood into the mechanic energy of muscular contractions and heat. The mechanic energy keeps the entire mass of blood in the body in constant motion throughout the blood-vessels, which form a system of closed elastic tubes. The blood forced into the arteries by the rhythmic contractions of the ventricles of the heart meets with a considerable degree of friction in the constantly narrowing arterial branches, and the resistance thus produced gives rise to the intravascular blood-pressure. This blood-pressure depends for its production and its degree upon the force of the heart's contractions and the amount of resistance in the arteries, the latter varying by virtue of the contractility of the arterial walls. Under normal conditions the force of the heart's contractions is so adjusted that, speaking in general terms, there ensues a gradual fall of hemodynamic pressure in the direction of the blood-current—namely, from the arterial to the venous orifices of the heart—and in this manner there is established a constant flow of blood throughout the arteries, capillaries, and veins.

The intravascular pressure varies from time to time within normal limits, depending upon the degree of arterial contraction. Under the regulation of the nervous system, the amount of blood sent to an organ is determined by the degree of local arterial tension, and is increased or diminished according as its cells are the seat of functional activity or of physiologic rest. And the blood by its own weight gives rise to a certain degree of purely hydrostatic pressure, which will vary according to the position of the body and the varying height of the column of blood supported by the vessels, especially the veins. But in health the nervous regulation of the tonic contraction of the vessels is so precise that the equilibrium of the circulation is not disturbed by changes in the hydrostatic pressure.

The circulation may be thrown into disorder in various ways. In the first place, there may arise general disturbances which affect all parts of the vascular system, and result in derangement of the onward movement and distribution of the general mass of blood and lymph. Then there are various local disturbances that only influence small vascular districts. Many local disorders react upon the circulation in general, but often in so slight degree as to escape observation.

GENERAL CIRCULATORY DISTURBANCES.

The general circulatory disturbances may arise (*a*) from conditions that interfere with the normal activity of the heart; (*b*) from diseases of the walls

of the blood-vessels ; and (c) from changes in the amount and composition of the circulating fluids.

General Circulatory Disturbances due to Disorders of the Heart.—Normally the heart in a given time transmits the same amount of blood from each of its cavities. It is quite evident that if the left ventricle were to expel, for only a short time, one cubic centimeter less blood with each contraction than the other chambers, the blood would accumulate in the pulmonary circuit, and death would rapidly follow from the fall of pressure in the aorta. While momentary variations may occur, yet the amount of blood brought to the heart and the amount sent away must balance in the long run or life cannot be maintained.

Now, disturbances of the circulation due to diseases of the heart all depend upon derangement of the heart's function in the sense that less blood is transmitted than received. The diseases of the heart to be considered in this connection become dangerous to the degree that they diminish the product of the heart's labor—*i. e.*, the amount of blood sent out. Diseases of this kind may be situated in the valvular apparatus of the heart—the usual result of the various inflammatory processes in the valvular endocardium is to render the valvular orifice narrower than normal or the valves incompetent. Let us consider for a moment the effect of a permanent narrowing of the mitral orifice: the left auricle is unable to send through the narrowed orifice the usual amount of blood. The result is an accumulation of blood in the pulmonary circuit and a falling off in the amount that reaches the systemic circulation. A disturbance has been created in the onward movement of the blood, which, unless counteracted, is bound to become serious. If an aortic valve is incompetent, it allows some of the blood sent into the aorta during each diastole to regurgitate, the consequence being a diminution in the blood forwarded from the left ventricle. Indeed, so much blood may accumulate in the pulmonary circuit that the right heart is prevented from transmitting through the lungs the same amount that it receives, and there results a further massing up of the blood in the systemic veins. Similar effects would eventually follow stenosis or valvular inefficiency at any of the orifices of the heart. The general result of stenosis of an orifice or of incompetency of a valve will be, then, an accumulation of blood in the pulmonary or systemic veins—a general venous hyperemia—and a diminution of blood in the systemic arteries—an arterial anemia—due to the fact that less blood is sent away from the heart than is brought to it.

Diseases of the myocardium may have essentially the same effect. If for any reason, such as degenerative lesions in the heart's muscle, anemia, or other changes due to diseases of the coronary arteries, the contractions become irregular and enfeebled, so that the usual amount of blood is not sent into the arteries, it will follow that the pressure in the arteries sinks, while the blood accumulates on the venous side.

Diseases of the pericardium, accompanied by extensive adhesions between the two layers, or by the accumulation of fluid in the pericardial sac, cause serious disorder of the heart's action. In the case of adhesions these may be so strong as to prevent complete ventricular contraction, and in the case of fluid accumulations the pressure upon the heart may prevent full diastole. In either case the action of the heart becomes insufficient to keep up the equal distribution of the blood-mass, and venous hyperemia and arterial anemia result. Pressure upon the heart by undue elevation of the diaphragm, or

dislocation of the heart from this or other causes, may also result in cardiac insufficiency.

Continuation of circulation under these circumstances depends, first, upon the power of the circulatory system to adapt itself to variations in the amount of blood; and, second, upon the efforts of the heart to restore the circulatory equilibrium by undergoing a compensatory enlargement or hypertrophy. Thus, stenosis of the mitral orifice brings about, as stated, an accumulation of blood in the pulmonary circuit and a diminution of the amount sent into the aorta. By contraction of the arteries the arterial pressure remains practically unchanged, and in the meantime the wall of the left auricle grows thicker and stronger—undergoes hypertrophy—and perhaps becomes able to force as much blood through the narrowed orifice in its systole as enters the auricular cavity during the diastole. In a similar manner the heart, for a time, may compensate more or less fully for the insufficiency of its labor caused by disease at any of the valvular orifices. But an hypertrophied heart is always in danger of failure to meet the constantly increasing demands upon its toil, and sooner or later cardiac insufficiency develops in an aggravated form.

Chronic cardiac insufficiency results in congestion of the venous systems, because less blood is sent away from the heart than is brought to it; and yet at first the resulting arterial anemia is not so great but that by the narrowing of the arteries sufficient pressure is kept up to maintain the circulation. Usually an increased pressure develops in the dilated veins, which is followed by increased transudation from the capillaries and by edema. In consequence of the diminished amount of blood sent out from the left ventricle there is slowing of the circulation in the capillaries, increased accumulation of carbonic oxid in the blood, shown by a bluish discoloration of the skin—cyanosis—and also a fall in the temperature of the external surface. If the amount of blood sent into the aorta is very small, disturbances follow in the regulation of the arterial tonus, the arterial pressure sinks greatly, and the blood may accumulate in the veins and capillaries of the dependent parts of the body, giving rise to a bluish discoloration called hypostasis. Hypostasis indicates that the hemodynamic pressure has fallen so low that the blood in the dependent parts of the body obeys the law of gravitation only. These conditions signify that the cardiac insufficiency is extreme, and liable to be followed by a cessation of the action of the heart.

After death the tension of the vessels disappears; the arteries contract somewhat in consequence of their elasticity. Coagulation of the blood does not occur at once, and the fluid blood, following the law of gravitation, accumulates in the veins and capillaries of the dependent parts of the body. Some of the plasma is forced through the dead and consequently more permeable capillary walls, and the red corpuscles fall more closely together. The skin of such portions of the body becomes deep bluish-red and the tissues moist. The discoloration may be absent over portions of the dependent surface that are compressed over the bony prominences upon which the body rests. In the pulmonary circulation the hypostasis shows itself in the form of deep bluish-red, congested districts in the dependent parts of the lung, the tissue here being also infiltrated with serous fluid. Hypostasis likewise occurs in the veins and capillaries of the pia mater.

General Circulatory Disturbances due to Changes in the Blood-vessels.—The normal elasticity of the walls of the blood-vessels

is a most important factor in regulating the flow of blood. The arteries of the body support an uninterrupted, though periodically diminishing and increasing, tension; in many individuals the muscular coat is so perfect as to permit of a continuous tension during a long lifetime without becoming overstretched or dilated.

The most important disease of the vessels (angiosclerosis) with respect to the consecutive circulatory disorders is due primarily to diminution or loss of elasticity in the vascular wall. When the arteries lose their elasticity, dilatation of the lumen and growth of connective tissue in the intima follow (Thoma), so as again to reduce the size of the lumen to the normal. The wall is now thicker and stiffer than before, and the blood flows through a less yielding tube offering an increased resistance to the current. In order to overcome this increased resistance the heart, at first in the left and then also in the right ventricle, undergoes hypertrophy. If the extent of the arterial disease increases, so that the intima becomes rough and the wall irregularly dilated and thickened, the increased resistance to the current, aided by nutritive disorder of the heart-muscle, may lead to development of cardiac insufficiency and its consequences.

Under certain conditions the peripheral arteries may contract persistently and give rise to increased peripheral resistance. This occurs as a transitory manifestation in carbon-dioxid poisoning. In chronic inflammatory diseases of the kidneys permanent increase of pressure arises in the systemic circulation, due to arterial contraction from obscure and complex causes, and cardiac hypertrophy results.

Congenital narrowing of the aorta, large thrombi upon its walls, and compression by tumors may all give rise to hypertrophy of the heart.

A diminution in the total peripheral resistance to the current in the systemic circulation may be caused by a fall of the arterial tension, due to paralysis of the vasomotor centers. This occurs when the cervical part of the spinal cord is destroyed. The arteries dilate rapidly, the blood flows into the veins quickly, there is a decrease in the difference between the arterial and the venous pressures, the stream becomes slower and slower, and the heart is not able by its contractions to bring the blood-pressure up to normal. The blood-pressure may fall so low that the blood, following the law of gravitation, sinks to the dependent parts of the body and forms areas of hypostatic congestion. These phenomena can be studied upon animals after cutting either the cervical spinal cord or the vagus and sympathetic nerves, and then employing artificial respiration.

In the pulmonary circulation increased resistance to the current may be brought about by all those conditions that hinder respiration, such as pleuritic adhesions and curvature of the spinal column. Compression of the lungs by fluid accumulations in the pleural cavities, and diseases of the lungs accompanied by extensive destruction or removal of lung-substance and consequently of its capillary districts—emphysema, chronic interstitial and tuberculous processes—also cause obstruction to the circulation through the lungs. Such obstruction increases the pressure in the pulmonary artery and in the right heart, and gives rise to hypertrophy of the latter; if the hypertrophy cannot overcome the obstruction, passive congestion of the systemic venous circulation results.

General Circulatory Disturbances due to Changes in the Amount and Composition of the Circulating Fluids.—A gen-

eral acute anemia leads to a transitory fall in the aortic pressure, which rapidly rises again, if the loss is not too great, by the accommodation of the arterial tension to the reduced volume of blood (see Hemorrhage, page 50), and by a rapid restoration of the former volume of the blood-mass by an increased absorption of fluid from the tissue-spaces.

In chronic anemia (oligemia, oligocythemia) the arterial pressure is usually lessened and the blood-current is slowed. The absence of the normal amount of oxygen in the blood may lead to fatty and albuminous changes.

Hydremia, or hydremic plethora, an increase in the water of the blood, develops in chronic and acute diseases of the kidney, associated with a diminished excretion of water in the urine. It is usually associated with edema or dropsy, due to increased transudation through the changed walls of the capillaries and the accumulation of plasma in the tissue-spaces.

Anhydremia, or the diminution of water in the blood, occurs as a consequence of profuse watery evacuations in acute, severe intestinal catarrhal inflammations and in Asiatic cholera. It leads to the production of a small, slow pulse, due to the fall of arterial pressure, and also to diminution in the secretion of urine and saliva; the skin becomes dry and wrinkled, cold and cyanotic. These changes are in part attributable to the slowness of the circulation, in part to diminution in the total amount of circulating fluid.

PATHOLOGIC VARIATIONS IN THE LOCAL AMOUNT OF BLOOD.

The amount of blood required by an organ or tissue is subject to considerable variation within physiologic limits, according as the cells are functionally active or dormant. The regulation of the blood-supply under these circumstances is accomplished by changes in the caliber of the arteries, the smooth muscle-fibers of which contract or relax, as the case may require, under the influence of the vasomotor nerves, while the normal elasticity of the arterial wall maintains the necessary tone. An organ rich in blood is described as hyperemic, while one containing but little blood is spoken of as anemic.

When the amount of blood in an organ or limited vascular territory exceeds or falls below the physiologic limits, occurring independent of physiologic causes, or persists for an abnormal length of time, then the condition becomes one of pathologic hyperemia or anemia.

Pathologic hyperemia of an organ may result either from an excessive supply of arterial blood, in which case the state is known as arterial, active, or congestive hyperemia; or it may result from obstruction to the outflow of the venous blood, when the hyperemia is designated as passive, or venous.

Arterial, or Active, Hyperemia.—Active hyperemia is due to an increased supply of arterial blood. It may occur under a variety of circumstances, different causes producing dilatation of the arteries of a vascular territory either by paralyzing the vasoconstrictor nerves, by stimulating the vasodilator nerves, by directly weakening and paralyzing the muscular coat, or by removing or diminishing the extravascular pressure. The action of the following substances and conditions may lead to arterial hyperemia.

Chemicals.—When the frog's tongue or the mesentery of the rabbit is irrigated with a 1.5 per cent. salt solution, arterial dilatation and active hyperemia occur (Thoma¹). There are a number of medicinal substances,

¹ *Allg. path. Anat.*, p. 388.

such as alcohol, ether, ammonia, mustard, cantharides, etc., which when applied to the skin or mucous membranes cause local hyperemia. Some of these substances produce after more prolonged contact not merely simple hyperemia, but also hyperemia accompanied by exudative processes and the formation of vesicles.

Local Mechanic, Traumatic, and Thermic Influences.—It is within daily experience that scratching the skin produces red areas. In certain diseases of the nervous system, such as *tabes dorsalis*, meningitis, etc., also in exophthalmic goiter, very light strokes often suffice to produce red stripes and spots (dermographia in exophthalmic goiter; *tâches cérébrales* in meningitis). In these experiments the irritation of the skin produces circumscribed arterial hyperemia by modifying the vasomotor innervation. The exact mechanism by means of which the hyperemia is produced is not clearly understood, but the fact that in diseases of the central nervous system hyperemic areas so easily appear would seem to indicate that the local irritation of the skin acts in a reflex manner.

More severe trauma also produces local arterial hyperemia, usually accompanied by further changes, that are considered elsewhere. Moderate heat when applied to the skin leads to vascular dilatation and hyperemia, even when the nerves connecting the arteries with the cerebrospinal vasomotor centers have been completely severed.

Local anemia, when not altogether too evanescent, is usually succeeded by arterial hyperemia. Local anemia produced by the application of cold is regularly followed by a brief hyperemia when the normal temperature of the part is again restored. The removal of long-continued pressure upon blood-vessels is also succeeded by arterial dilatation and hyperemia, which may give rise to a secondary, or collateral, anemia elsewhere in the body; the collateral cerebral anemia occasionally produced may give rise to fainting. This is sometimes the result of the great hyperemia of the blood-vessels of the abdomen that develops when large fluid accumulations are suddenly removed by tapping, unless the pressure previously exerted by the fluid is in a measure replaced by means of a tight abdominal bandage. The production of arterial anemia in practical surgery by the application to an extremity of an Esmarch bandage is succeeded by arterial dilatation after the removal of the constrictor.

The closure or narrowing of an artery leads to a collateral hyperemia of neighboring areas (page 44).

Paralysis of the vasoconstrictor nerves produces a pure arterial hyperemia. Cutting the sympathetic nerve in the neck of animals is followed by arterial dilatation and redness in the corresponding half of the head and neck: wounds and pressure by tumors, glands, etc., have the same effect in man. Reflex vasomotor influences of various kinds also lead to hyperemia, as, for instance, in blushing.

In consequence of the dilatation of the arteries in active hyperemia, the blood-current meets with less resistance than normally, and a greater amount of blood flows through the hyperemic area. The pressure in the corresponding capillary district rises as the blood remains under a greater hemodynamic pressure, on account of the diminished peripheral arterial resistance. In this way may be explained capillary and venous pulsation, which is sometimes observed in actively hyperemic parts. The rise of pressure in the capillaries leads to dilatation of the latter, and a diffuse redness develops.

The exact influence of hyperemia upon the process of transudation has not yet been determined. Emminghaus states that in occasional instances there was an increased production of lymph in the dog's leg, made hyperemic by cutting the sciatic nerve.

During life the hyperemic area is of a more or less deep-red color, and, if located upon the surface of the body, is warmer than its surroundings; but arterial hyperemia is not demonstrable after death.

Local Venous Hyperemia.—Local venous hyperemia, or passive congestion, arises from obstruction to the outflow of the blood from the veins of an organ or vascular territory. It may be part of a general venous congestion due to central causes, located in the heart, mediastinum, or lungs; or it may depend upon purely local circumscribed conditions.

Among the various causes of strictly local passive hyperemia may be mentioned external compression of the veins by tumors, aneurysms, contracting cicatricial tissue, inflammatory swellings, and ligatures; occlusion of the lumen of the veins by ingrowing tumors, by thrombosis, and, in rare instances, by embolism; increased pressure in the abdominal cavity by large tumors, excessive ascites, and by the pregnant uterus.

In all these instances the general effect of the obstruction will naturally vary, depending upon the degree and the anatomic seat of the hindrance, and upon the absence or presence of collateral routes along which the returning venous blood, circumventing the obstruction, may reach the heart. If the occluded vein communicates quite freely with other veins, then the obstruction will cause at most only a temporary overfilling of the veins drained by the blocked vessel, the blood soon finding exit by way of the communicating branches. But if the obstructed vessel possesses insufficient or perhaps no communications with other veins, then the phenomena of passive congestion will develop to the fullest degree. Among veins and venous channels belonging to the latter group may be mentioned the splenic, the renal, the femoral, and the portal vein, and the sinuses of the dura mater.

The phenomena of passive congestion can be observed by making the following experiment (Cohnheim¹): A frog is curarized and the two lateral veins of the tongue ligated near the root of the latter; in this way all the collateral branches are shut off. The appearances can now be studied from time to time by spreading the tongue out, and fastening it by means of pins to strips of cork glued to a glass slide. At intervals the tongue should be returned to the mouth, lest excessive vascular changes occur. Marked congestion rapidly develops; the veins and capillaries dilate; the tongue becomes dark red; the distinction between the axial and the peripheral currents in the veins is lost. These and the capillaries become crowded with closely packed red blood-corpuscles, whereas the blood-plasma seems to disappear, while the tongue becomes slightly swollen. In the course of a few hours the blood has stopped in the veins and capillaries—*stasis*—and a few red corpuscles have found their way out of the vessels into the surrounding tissue-spaces—*diapedesis*; while in the arteries the blood-mass presents oscillatory movements synchronous with the pulse. Here and there near the root of the tongue are seen greatly dilated capillaries, hitherto invisible, through which the blood very slowly finds its way into the unobstructed veins, thus relieving in a small degree the congestion. According to Thoma

¹ *Virchow's Archiv*, xli., 1867.

and Zielenko, the arteries are not dilated, but contracted, in this and similar experiments.

From experiments and clinical observations it has been learned that obstruction to the venous outflow causes first a slowing of the current in the veins and the capillaries on the distal side of the hindrance. The slowing of the current lessens the resistance due to friction; hence, less hemodynamic pressure is consumed, and a rise of pressure ensues in the veins and capillaries of the congested area, causing them to dilate. The increased pressure favors transudation of serum, and this may occur to such an extent that the lymph-vessels are not able to carry away the transudate accumulating in the tissue-spaces, and a condition of edema, or dropsy, develops. The contraction of the arteries in the congested area is secondary to the diminished amount of blood that flows through this area in a given time; it tends to prevent an excessive rise of pressure in the veins and capillaries, and to limit the amount of transudation, while the collateral veins are given time to dilate, and thus to relieve the congestion.

In passive hyperemia of an extremity the tissues become swollen on account of the dilatation of the capillaries and veins and the increased transudation; the cutaneous surface is cool, because less blood passes through the congested part and less heat is brought to it; a bluish discoloration of the skin, so-called cyanosis, develops, because the blood in the capillaries is rich in carbonic oxid by reason of the sluggish circulation. These conditions may persist for a long time, especially when the hyperemia is of central origin, and may result in thickening and increase of the subcutaneous, inter-muscular, and even periosteal connective tissue.¹

In the internal organs moderate degrees of passive congestion of short duration do not, as a rule, produce permanent changes. When of long duration the pressure of dilated capillaries upon adjacent cells may cause a degenerative atrophy. Diapedesis of red blood-corpuscles may also take place, followed by disintegration and the setting free of pigment-granules. Under these circumstances some increase of the connective tissue generally results.

The severest form of passive congestion develops from occlusion of all the efferent vessels of an organ or an extremity. Here the rise of pressure in the veins and capillaries may equal the pressure in the arteries. All the plasma of the blood may pass out into the tissues, and complete stasis or stoppage of the blood-flow may result. The changed capillary walls favor diapedesis, and the tissues become the seat of a bloody infiltration, or hemorrhagic infarction, followed by death of the hemorrhagic area. Decomposition, or moist gangrene, may develop in the dead tissues.

Complete closure of all the veins of an organ may occur in the case of the spleen, liver, or kidney, in consequence of thrombosis or retrograde embolism. In a case of complete thrombosis of all the veins of the spleen observed by the writer, hemorrhagic infiltration and necrosis of the entire organ ensued. When branches of the splenic (Sokoloff) or renal (Litten) vein are ligated, circumscribed necrotic areas are formed that become infiltrated with blood, just as in the case of hemorrhagic infarcts due to arterial occlusion. Arnold demonstrated that retrograde embolism of the hepatic vein gives rise to hemorrhagic infarction in the liver.

¹ The student can readily observe the ordinary initial phenomena of passive congestion in an extremity by encircling a finger with a tight rubber band: the coolness, the swelling, and the discoloration all occur.

In strangulated hernia the imprisoned loops of intestine become the seat of a marked passive congestion which may be succeeded by stasis, hemorrhagic infiltration, and necrosis.

In the case of the portal vein certain anomalous conditions are presented, because of its breaking up into capillaries within the liver before emptying, by way of the hepatic veins, into the vena cava. Obstruction to the blood-flow in the portal vein may occur not only in the course of the vein proper, but also in the substance of the liver. While sudden occlusion of the portal vein in animals is almost immediately fatal, in man sudden closure from thrombosis is not followed by rapid death. The pressure in the vein rises rapidly, the branches and radicles dilate excessively, large quantities of serum transude into the abdominal cavity, the spleen increases to three or four times its normal size, watery discharges take place from the bowels, and death finally occurs from exhaustion. In some of the forms of cirrhosis of the liver the contracting fibrous tissue compresses and destroys the portal branches and capillaries, so as to cause obstruction and passive congestion of the portal vein and its radicles. Usually this occurs so slowly and gradually that in many cases a collateral circulation has time to develop by means of the rather inconstant anastomosis between radicles of the portal vein and the esophageal, hypogastric, and other veins; in the majority of instances, however, the pressure remains high enough to result in ascites and in marked congestion of the spleen and the gastro-intestinal tract.

In the lungs chronic passive congestion, with induration and pigmentation, may follow disease in the mitral valve or insufficiency of the muscle of the left ventricle.

Local Anemia (Ischemia); Collateral Anemia; Infarction.—

Local anemia is due to a diminished amount of blood in a vascular territory. It may be part of a general lack of blood in the body, or it may depend entirely upon local causes, such as external compression of the arteries and capillaries, narrowing or closure of their lumen from changes in their interior, or increase of the normal peripheral resistance to the current by contraction of the circular muscular coat. Thus, local anemia is produced by compressing the vessels of an extremity with an Esmarch bandage, by the pressure of a tumor, of an extensive inflammatory exudate, or of contracting cicatricial tissue on the arteries. Or it may follow the narrowing or occlusion of the lumen of an artery by inflammatory thickening of its walls (endarteritis), by the formation of thrombi, or of the lodgement of emboli in its interior.

Disturbances of the vasomotor innervation often produce local anemia, as shown, for instance, by the bloodless condition of the body surface when exposed to cold. Brown-Séquard showed that stimulation of the cervical sympathetic is followed by contraction of the arteries of the same side of the head. A so-called collateral anemia, due to arterial contraction, usually develops in the vicinity of areas in which arterial dilatation and hyperemia prevail, and in the case of excessive active hyperemia of an organ or part distant parts may become anemic. Under such circumstances the total quantity of blood is not sufficient to fill all the vessels to the usual extent.

Local anemia produces paleness of the affected tissues. The narrowing of the arteries increases the resistance to the current, and in order to overcome the resistance more hemodynamic pressure is used, and the blood reaches the capillaries under lower pressure; the capillaries contract in consequence of their elasticity and the fall in pressure, and the total quantity of blood in the

area diminishes. In the skin the anemic part is of a lower temperature than the surrounding integument, because with the lessened amount of blood less heat is brought to the surface.

Anemic conditions produced by tonic contraction of the arteries are usually temporary in duration; but the occlusion due to ligatures, thrombosis, or embolism, being often permanent, results in nutritive disturbances or the formation of new routes for the circulation.

According to Thoma and Nothnagel, occlusion of an artery leads to arrest of the circulation in the area after the vessel has emptied itself; the pressure rises a little from the point of the obstruction back to the nearest arterial branch. If the branches distal to the obstruction possess free communication with an unobstructed artery, the latter becomes somewhat dilated, and the circulation is soon restored through the area nourished by the occluded vessel. The rapidity and the completeness with which the collateral circulation develops depend upon the size and capacity for dilatation of the branches that are in communication with the vessels of the anemic area. If numerous and large, the circulatory disorder is soon obviated. If this be not the case, then more complex, but exceedingly interesting, changes of adaptation develop. A contraction of the occluded artery occurs proximal to the point of obstruction; in the collateral arteries increased rapidity of the current and dilatation of the lumen take place, giving rise to a vicarious hyperemia. The vessels through which the collateral circulation is being established soon show actual increase not only in the thickness of their walls, but also in length, becoming somewhat convoluted; while the central, patent part of the occluded artery becomes the seat of a concentric atrophy, with narrowing of the lumen. In other words, the intravascular pressure is readjusted so as to favor the development of collateral circulation; while in the arteries such structural changes take place as render them best adapted to meet the new requirements.

The mechanism of these changes is in part as follows: When a main artery is ligated the blood flows with little resistance from the capillaries of the anastomosing branches into those of the ligated artery, the result being an increased rapidity of flow in the anastomosing vessels (von Recklinghausen). The resulting changes in the walls of the arteries are best interpreted as referable to a genuine work-hypertrophy (Welch).

It has also been shown that new anastomoses may be formed by the capillaries, which dilate and gradually acquire the structure of arteries. Even veins may be forced into service: the blood above a ligature flows into a capillary district, and thence into a vein, which again allows the blood to pass into the capillaries of arterial branches below the ligature.

Under certain special local conditions the closure of an artery fails to be followed by an efficient collateral circulation, and the consequence is that the part formerly nourished by the occluded vessel undergoes necrosis due to ischemia. It is in the organs supplied with so-called *terminal arteries* (Cohnheim¹) that anemia has this result (see page 72, concerning embolism in this connection). An end-artery, or terminal artery, is an arterial branch which supplies a definite portion of an organ, and has no anastomosis with neighboring branches. Such arteries are found in the spleen, the myocardium, the kidney, the brain, certain parts of long bones, and the retina. The superior mesenteric artery and pulmonary arteries also possess imperfect

¹ Virchow's Archiv, lxx., 1875.

collateral communications, and act, particularly under special conditions, as virtual terminal arteries.

The anemia resulting from occlusion of a terminal artery leads to death of tissue, in some organs earlier, in others later: ganglion-cells, renal and intestinal epithelial cells perish if the circulation is interrupted for two hours; while skin, bone, and connective tissue may live without blood-supply for twelve hours or longer. The areas of anemic necrosis following the occlusion of terminal arteries are called *infarcts*. They are most typical in the spleen and in the kidney; here they present a pyramidal or wedge-shaped outline, the base corresponding to the surface of the organ, the apex pointing inward. At the point is usually found the plugged artery (Figs. 1, 2).



FIG. 1.—Anemic embolic infarct in the cortex of the kidney. The embolus was a small thrombotic mass detached from a heart-valve the seat of inflammation.

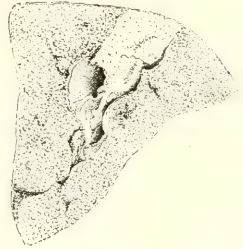


FIG. 2.—Irregularly pyramidal-shaped anemic infarct in the spleen, with softening about the apex, due to embolism of the splenic artery.

On the cut surface the infarct presents an opaque, yellowish-white appearance; microscopically, in stained sections, the nuclei of the cells are found wholly or partially unstained—necrosis, or death, has occurred.

As long as the infarct remains bloodless it is designated an anemic, or white, infarct, in contradistinction to the red, or hemorrhagic, infarct which is produced when blood reenters the previously bloodless area. This blood does not come, as a rule, from arterial anastomosis, but from neighboring capillaries; regurgitation from the veins probably does not occur. The fact that this blood appears in the area of anemic necrosis may be regarded as of the nature of an effort to establish a collateral circulation, but the obstacles are so great that in the meantime the tissues die; furthermore, the interruption of the circulation results in such alterations of the capillary walls that all parts of the blood, solid as well as fluid, pass out and infiltrate the surrounding dead tissue. In this way the hemorrhagic infarct is produced. Even should the blood enter the capillaries of the anemic area early, the low pressure under which it is is insufficient to reestablish the circulation. According to Thoma, the blood is prevented from entering the vessels of anemic areas in the spleen by the temporary tonic contraction of the smooth muscular fibers in the trabeculae of the organ.

Some infarcts are only partly hemorrhagic, for the dead tissue may offer so much resistance to the flow in the capillaries that it is arrested; this is frequently observed in the kidney. According to Litten, hemorrhagic infarcts may develop in the kidney after ligation of the corresponding vein, showing that the blood in question must come from the surrounding capillaries.

In the brain, occlusion of the smaller vessels beyond the circle of Willis is followed by necrosis, with liquefaction or softening of the brain-tissue. These areas of softening may present variations in color, depending upon small hemorrhages into the necrotic tissue from the surrounding capillaries.

The superior mesenteric artery anastomoses to a certain extent with the inferior mesenteric and with the gastroduodenal arteries; but these anastomoses are not sufficient to reestablish after occlusion the circulation with sufficient rapidity to maintain the integrity of the capillary walls (Litten).¹ The anemia, aided by the action of the intestinal bacteria and their toxic products, results in extensive necrosis; and when blood enters by way of the collateral channels mentioned hemorrhagic infiltration of a large part of the intestine develops. Peritonitis, septic intoxication, and death may follow. The slower occlusion of the artery by thrombosis may give the collateral circulation greater time to develop, and such extensive necrosis may be in part, or even wholly, prevented. Hemorrhagic infarction and necrosis of the small intestine are also observed in connection with thrombosis of the portal or the mesenteric vein (Riesman).²

The coronary arteries of the heart also possess collateral branches that are insufficient to prevent anemic necrosis of the heart-muscle following occlusion due to embolism, thrombosis, or other causes. Some hemorrhage usually occurs into the necrotic and softened tissue.³

In the lungs hemorrhagic infarcts (Fig. 3) occur most readily under special local conditions, namely, when the lung is the seat of passive



FIG. 3.—Irregularly wedge-shaped embolic hemorrhagic infarct in the lung, following thrombosis in the right auricle, in a woman with mitral stenosis. The border is sharp; the area quite homogeneous and red.

congestion, which is most frequently due to disease of the mitral valve. In that case embolism or thrombosis of the pulmonary arteries gives rise to infarction. The pressure of the blood in the adjacent capillaries, which under ordinary conditions may be sufficient to restore the circulation through the obstructed area, is unable to overcome the greatly increased venous pressure due to the valvular disorder, and stasis, transudation, diapedesis,

and hemorrhage occur. In very rare instances pulmonary infarcts are anemic in consequence of extreme weakness of the circulation (Welch).

Hemorrhagic infarction and necrosis of the uterus may follow bilateral embolism of the hypogastric arteries or bilateral thrombosis of the uterine veins (Chiari).⁴

Anemic and hemorrhagic infarcts are most frequently produced by embolism. In case the embolus is infected suppuration usually occurs. The consequences of infarction due to aseptic emboli depend upon the part affected: if in the brain, the retina, the heart, etc., serious functional disturbances may follow. The further changes are those of absorption and replacement with connective tissue (Fig. 4) or, in the case of the brain,

¹ *Virchow's Archiv*, lxx., 1875.

² *Prag. med. Woch.*, 1896.

³ *Proc. Path. Soc. Phila.*, vol. ii., N. S.

⁴ Baumgarten, *Am. Jour. Phys.*, 1899.

cyst-formation. Extensive infarcts too large to be absorbed may become calcified and enclosed in cicatricial tissue.

STASIS.

Stasis develops when the blood in the capillaries loses all its plasma. The capillary lumen becomes distended with a homogeneous, dark-red column or mass of red blood-corpuscles, which are so closely crowded together that the contour of the individual corpuscles is no longer distinguishable. Thrombosis as a rule does not occur, and the red corpuscles do not coalesce into one mass; and when the conditions that resulted in stasis are removed and plasma again enters the capillaries the corpuscles gradually separate from one another, so that the normal blood-current is soon restored.

Stasis arises under a number of different conditions that are usually connected with the various forms of local circulatory disturbances. Thus, excessive passive hyperemia due to complete obstruction to the venous current

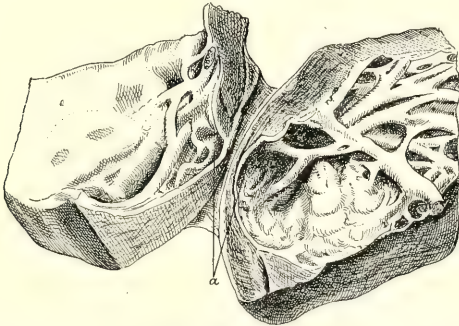


FIG. 4.—Absorption of necrotic tissue, due to arterial occlusion in the wall of the left ventricle, the formation of connective tissue, and beginning bulging of the wall at the weak place (a).

will result in such dilatation and rise in pressure in the capillaries, veins, and arterioles of the congested area that the blood-plasma is pressed out through the capillary walls into the meshes of the tissue (edema), while the red corpuscles come into closer and closer apposition.

In inflammation and in local anemia following embolic and other forms of arterial occlusion, stasis also develops as a result of nutritive changes in the capillary walls, which present such increased permeability that the plasma pours out from the vessels.

Stasis may be produced by the action of chemical and other influences upon the tissues. Thus stasis may result from evaporation and drying of tissues that are brought out from the interior of the body and exposed to dry air. Cold and heat may cause stasis; so also the action of acids and alkalies, of chloroform and alcohol, of croton oil, etc. These substances may act in different ways: by abstracting water, by changing the capillary walls so as to increase their permeability, or by making the red blood-corpuscles viscid. Concentrated solutions of sugar and of salt (5 per

cent.), when applied to the tongue or mesentery of frogs, produce stasis by removing the water from the circulating blood (Wharton Jones,¹ von Recklinghausen).

HEMORRHAGE.

Hemorrhage is the exit of the blood from the circulatory channels. It may occur from the capillaries, veins, arteries, or the cavities of the heart; and the blood may escape externally upon the skin, into mucous or serous cavities, or into the interstices of the tissues.

The blood may pass out from the vessels in two ways, either by *diapedesis* or by *rhesis* (diabrosis). *Diapedesis* is the passage of the red blood-corpuscles and of the plasma through the unruptured walls of capillaries and minute veins. Hemorrhage by *rhesis* is hemorrhage in consequence of mechanic solution of continuity of the vessel-wall; it is the only way in which hemorrhage can take place from the heart, the arteries, and the larger veins. From the minute veins and the capillaries bleeding may occur in either way.

In order to study the process of diapedesis, a vein in the mesentery or tongue of a curarized frog may be ligated, so as to produce passive congestion and stasis (Cohnheim). After a certain time the red blood-corpuscles begin to pass out from the capillaries and venules into the surrounding tissues. The microscopic appearances of the capillary walls in the living animal do not present any deviations from the normal under these circumstances. If the ligature, the cause of the stasis, be removed and the circulation allowed to become natural again, the details of the process can be studied even better than before. The red cells are noticed not only in the tissues, but also in the capillary walls, where they are seen, either singly or in groups, lying compressed in small openings. From time to time a corpuscle will be seen to attach itself to the inner surface of a capillary, a fine process passing outward through the wall. As the extravascular process becomes larger the intravascular part becomes smaller and smaller, until finally the whole corpuscle has passed through into the tissues, where it soon resumes its normal form. Only a few corpuscles become broken into fragments, the majority pass through uninjured. A few white cells and some blood-plasma also pass out.

Thoma has observed that in warm-blooded animals even a thicker blood-stream may pour out through an opening in the capillary wall, which immediately closes itself again. In consequence of such streaming out by diapedesis quite extensive areas of hemorrhage (ecchymoses) may form in the mesentery.

Diapedesis was first observed by Stricker and by Cohnheim; subsequently it was studied by Arnold,² whose investigations disclosed the finer details of the process. Arnold injected silver-nitrate solutions into capillaries the seat of diapedesis, and found that at points the silvered borders of the endothelial cells presented changes which he regarded as minute openings, called stigmas, or stomas. Subsequently he regarded these points as due to a greater accumulation of cement-substance between the endothelial cells, and concluded that diapedesis occurs as a consequence of an increased permeability of the capillary wall, best explained as due to a loosening of the intercellular cement-substance. Inasmuch as the red blood-corpuscles are

¹ *Guy's Hosp. Reports*, 2d series, vii.

² *Virchow's Archiv*, lviii., 1875.

immobile, it would seem that they are pressed through the capillary wall by the intracapillary blood-pressure.

Hemorrhage by diapedesis may reach a considerable extent, especially when it takes place in a large area and continues for a long time.

Diapedesis occurs frequently in consequence of local circulatory disturbances which produce changes in the vascular walls, namely, in local anemia with subsequent formation of hemorrhagic infarction (page 45), in passive congestion and stasis, and also in inflammation. Diapedesis, furthermore, accompanies a number of general infections, intoxications, and nutritive disturbances, in which frequent spontaneous hemorrhagic extravasations indicate a widespread abnormal permeability of the capillary walls.

Hemorrhage by rhexis, or tearing of the vascular wall, may take place either spontaneously or in consequence of traumatism. Injuries of various kinds may give rise to hemorrhage by immediate severing of the walls of the vessels, as well as of the heart. Extensive and complex traumatisms, accompanied by twisting and distortions of the body, are often the cause of hemorrhage far removed from the location of the direct injury. Such hemorrhages may be either capillary, venous, or arterial, according to the kind of vessel affected; in a large number of conditions the blood comes from all three divisions at the same time. The so-called parenchymatous oozing which occurs from the surface of an operative wound after the larger vessels have been ligated is a good example of traumatic capillary hemorrhage. When blood escapes externally from an artery it spurts forth intermittently, whereas from a vein the flow is more continuous. The extent of an unhindered traumatic hemorrhage will depend upon the size of the severed vessels as well as upon the extravascular conditions. Thus a small vessel upon the surface of a large cavity will give rise to more bleeding than a similar vessel in the interior of a solid organ, where the pressure after a time may be sufficient to arrest further flow.

In persons suffering from hemophilia (see below) insignificant wounds may be followed by persistent, sometimes uncontrollable, hemorrhage.

Spontaneous hemorrhage occurs in consequence of excessive rise in the blood-pressure, and as the result of diseases of the vascular walls. While increase in the intravascular pressure may cause rupture of a healthy capillary wall with capillary hemorrhage, it is the general opinion that increased intravascular pressure alone is not sufficient to rupture healthy, fully developed arteries and veins. Diseased blood-vessels may, of course, rupture under the normal vascular pressure; but a sudden increase of the pressure is the common exciting moment in the bursting of a pathologic vessel. Newly formed vessels, as in granulation-tissue and in sarcoma, break very easily.

The morbid changes which diminish the strength of vessels may develop primarily in the walls of the vessels, as inflammation, sclerosis, aneurysm, and fatty degeneration; or they may invade the wall from without, as is seen in various inflammatory and destructive processes. Hemorrhage produced in the latter instance is sometimes referred to as hemorrhage by diabrosis; a



FIG. 5.—Silvered capillary of a frog after diapedesis (Arnold).

good example is the hemorrhage of pulmonary tuberculosis, which is often caused by the rupture of a vessel the wall of which has been weakened by tuberculous invasion. Cerebral apoplexy, or hemorrhage into the brain, is a frequent and very important example of bleeding due to the rupture of arteries the walls of which have become weakened by primary disease.

Any sudden rise of intravascular pressure, such as may be caused by a comparatively unimportant trauma, straining at stool, sudden physical exertion, or fright, may precipitate the rupture of such weakened structures; and when a constant increased arterial pressure exists, as in chronic nephritis and hypertrophy of the heart, the danger of rupture of a diseased blood-vessel is always imminent.

Fatal hemorrhage may be caused by rupture of the heart, following softening or fatty degeneration of its muscle.

Certain individuals present a remarkable inherited or acquired tendency to hemorrhages, which is known as the hemorrhagic diathesis. In the hereditary form, termed *hemophilia*, or bleeders' disease, extensive, persistent, and sometimes uncontrollable hemorrhages follow traumatic lesions that in healthy persons give rise to but a transient and insignificant loss of blood. Protracted spontaneous hemorrhages also occur. The characteristic feature of hemophilia is not only the great tendency to bleeding, but also the absence or failure of arrest of hemorrhage by vascular contraction and thrombosis, which occurs in all smaller hemorrhages in the healthy. While the causes of hemophilia are unknown, theoretically the existence of abnormally constructed blood-vessels, as well as of a changed composition of the blood, causing a diminution in its coagulability, would explain the increased tendency to and the persistence of the bleeding.

Acquired hemorrhagic diathesis presents itself first as one of the essential manifestations of apparently primary diseases (scurvy, morbus maculosus Werlhofii, purpura hemorrhagica), characterized by hemorrhages into the skin, the serous and mucous membranes, and the parenchymatous organs. The etiology of these diseases is not yet definitely established, and for the present the tendency to hemorrhage must be assumed to be due to changes in the blood-vessels, produced by toxic substances of unknown, possibly bacterial, origin, and perhaps associated with diminution in the coagulability of the blood.

Acquired hemorrhagic diathesis also appears in a more or less pronounced form as a secondary manifestation in a number of infections (septicemia, cholera, small-pox, endocarditis, anthrax, typhus fever), intoxications (snake-bite, phosphorus poisoning), and chronic diseases accompanied by grave disorders of nutrition (carcinoma, chronic nephritis, leukemia and other blood diseases). In these diseases spontaneous ecchymoses and larger extravasations appear in various parts of the body. They must be attributed to nutritive disturbances and changes in the vascular walls, especially of the capillaries, due in some instances to a direct microbic implantation; in others to an impaired composition of the blood.

There are some hemorrhages that are ascribed to changes in the vasomotor innervation of the vessels, and are consequently designated *neuropathic*. This applies to the hemorrhages of vicarious menstruation (nose, digestive tract, skin, mammary glands), as well as to hemorrhages into the skin, conjunctiva, and other mucous membranes in hysteric persons (hysteric stigmas). Furthermore, many severe cerebral lesions are accompanied by

gastric, intestinal, adrenal, or pulmonary hemorrhages, which seem to stand in some direct relation to the nerve-changes. Brown-Séquard, Vulpian, and others observed such hemorrhages after operations upon the brain and spinal cord; but the exact mechanism by means of which these hemorrhages are produced has not been demonstrated.

The spontaneous hemorrhages of the hemorrhagic diatheses and the hemorrhages of neuropathic origin are undoubtedly largely of a capillary nature; but whether produced by rhexis or by diapedesis cannot be definitely stated, although it is probable that diapedesis is to a large extent responsible.

It is customary to distinguish by special names the hemorrhages that occur from free surfaces, into serous or other cavities, and into the substance of organs. Hemorrhage from the nose is known as epistaxis, from the respiratory tract as hemoptysis, from the stomach as hematemesia, from the intestines as melena, from the uterus as metrorrhagia (profuse hemorrhage during menstruation as menorrhagia), and from the urinary organs as hematuria. Effusion of blood into the pericardium is designated as hemopericardium, into the pleural cavity as hemothorax, into the tunica vaginalis testis as hematocele, into the uterus as hematometra, into the Fallopian tubes as hematosalpinx. Hemorrhage into the spinal cord is termed hematomyelia. When hemorrhage occurs into the interstices of tissue in the form of small punctiform foci, it is known as ecchymosis, or petechia. When the extravasation is more extensive, not sharply circumscribed, and rather flat, it is spoken of as suggillation, or hemorrhagic suffusion. When the blood firmly infiltrates the tissue the condition is one of hemorrhagic infarction (see page 45); and when a roundish, tumor-like mass of blood accumulates in the subserous or subcutaneous connective tissue, it is sometimes called a hematoma.

The consequences of hemorrhage depend upon the quantity of blood lost, upon the place where the hemorrhage occurs, and upon the further changes that take place in the extravasation.

In the first place, hemorrhage, either external or into the larger body-cavities, may be accompanied by the loss of so much blood that death ensues from the great fall of pressure in the arteries or from cerebral anemia. The circulatory system is, however, able to provide, within certain limits, against the immediate dangers of hemorrhage. It has been shown that in the dog the pressure in the aorta remains unchanged so long as no more than from 2 to 4 per cent. of the body-weight of blood is removed—2 per cent. in the case of sudden, 4 per cent. in the case of more gradual, loss. Thoma¹ calculates that in man almost one-half of the normal quantity of blood may be lost from hemorrhage without either marked or permanent fall in the aortic pressure. It is estimated that the loss of blood to the extent of more than 3 per cent. of the body-weight is dangerous, and rapid losses from large arteries may cause death even before this limit has been reached. Great variations are presented in the different ages and sexes and by different individuals.

The dangers from the loss of blood are met in part by the readjustment of the vascular tonus—as the blood is removed the arteries contract, so that the pressure in them remains unchanged—and also by the increased absorption into the blood-vessels of fluid from the tissues and lymphatic channels, so that during hemorrhage the relative quantity of water in the blood—*i. e.*, its volume—increases. In this way the dangers from rapid fall of pressure

¹ *Untersuch. über die Histogenese und Histomechanik des Gefässsystems*, 1893.

are obviated to a certain degree. Furthermore, Alexander Schmidt has shown that during hemorrhage the coagulability of the blood increases; this favors thrombosis and arrest of the hemorrhage. The development of thrombosis is also aided by falling of the blood-pressure.

Further changes that have for their purpose the regeneration of the blood are considered elsewhere.

Serious consequences may also follow hemorrhage on account of the place where it occurs. Thus, a sudden hemorrhage into the pericardial cavity, though not at all dangerous on account of the quantity of blood lost, may produce death by direct pressure of the blood-mass upon the heart; and hemorrhages into the brain, which are always accompanied by more or less tearing and destruction of tissue, are dangerous to life not only on account of the possibility of demolishing certain vital nervous centers, but also on account of the great increase in the intracranial pressure to which the extravasated blood gives rise; hemorrhagic extravasations into or behind the pancreas may cause sudden death from pressure upon the solar plexus. In persons who have been subject to long-continued small losses of blood, as from tumors of the bladder, a sudden larger hemorrhage may prove fatal.

The subsequent changes in the extravasated blood are essentially those of removal and absorption. After hemorrhage into the serous cavities the blood may remain fluid for some time, especially in the pleural and the peritoneal cavities, and considerable absorption of the fluid blood may occur. After a time, however, coagulation usually takes place. Considerable diffusion of hemoglobin now occurs, and the surrounding tissues become temporarily bluish-green. Broken-down as well as entire red corpuscles are taken up by leukocytes and carried away. Part of the hemoglobin is transformed into various kinds of crystalline and amorphous pigments (see Pigmentation), which are carried away by leukocytes or remain where formed, the bluish-green color gradually changing to yellow and finally disappearing. The dead white cells and the fibrin undergo fatty and other obscure chemical changes that are accompanied by varying degrees of softening. In the meantime the surrounding connective tissue proliferates, numerous leukocytes are attracted to the clot, and it finally becomes more or less completely absorbed and replaced by newly formed connective tissue which subsequently changes into a pigmented cicatrix. The regional lymph-glands are usually swollen and filled with leukocytes containing detritus removed during the absorption of the clotted blood. In some localities, especially in the brain, the softening of the coagulated blood and tissue-detritus is followed by the removal of the solid particles, while the fluid becomes enclosed in a sac of connective tissue, constituting a so-called apoplectic cyst. In some cases partially absorbed clots in the interior of tissues become calcified; or a microbic infection may occur, and the softened and changed extravasation becomes mixed with pus.

LYMPHORRHAGE.

Lymphorrhage, or extravasation of lymph, does not occur so frequently and is not so important a process as hemorrhage. It arises as the result of solution of continuity in the course of lymph-vessels. Inasmuch as the pressure in the lymph-vessels is not much greater than that of the surrounding tissues, it follows that extensive extravasations of lymph can take place only externally or into the larger cavities. In large wounds, such as

are made in extirpation of the axillary and supraclavicular lymph-glands, considerable quantities of lymph may ooze out into the dressings from the cut lymphatics for a day or more ; but this transudation ceases spontaneously. When an opened lymph-vessel remains permanently patent, so that lymph continuously escapes, either externally or into a large cavity, the condition is known as lymphatic fistula.

Wounds of the thoracic duct, as well as rupture in consequence of obstruction, result in large accumulations of lymph either in the peritoneal cavity, giving rise to *chylous ascites*, or in the pleural cavity—*chylous hydrothorax*. Such conditions may be fatal on account of the disturbance of nutrition that follows when the chyle is prevented from entering into the general circulation.

Chyluria signifies escape of chyle with the urine. It occurs after invasion of the lymph-vessels of the abdominal cavity and the thoracic duct by a parasite, the *Filaria Bancrofti* (see page 346), which causes obstruction to the lymph-current and secondary dilatation and rupture of the lymph-vessels in the walls of the urinary bladder.

EDEMA.

The intercellular spaces of the tissues and the serous surfaces are bathed in a clear, watery fluid, or lymph, that passes from the blood through the capillary walls, and is again emptied into the blood by the lymph-vessels and the thoracic duct, a part also being reabsorbed by the veins.

This fluid, or lymph, is the result of diffusion and filtration through the capillary walls. The exact composition, which varies in different parts of the body, is, according to Heidenhain, materially influenced by active secretory processes on the part of the endothelial cells of the capillaries ; but physiologists do not agree that a definite secretory activity of these cells has been proved.

When the amount of transudation from the blood exceeds the absorptive power of the lymphatics, the result is an accumulation of clear, watery fluid in the tissue-spaces, which is termed *edema*, or *dropsy* (*hydrops*).

Accumulation of transudate in the abdominal cavity is known as ascites, in the pleural and pericardial cavities as hydrothorax and hydropericardium, respectively, in the tunica vaginalis as hydrocele, in the spaces of the pia-arachnoid as external hydrocephalus, and in the ventricles of the brain as internal hydrocephalus. A universal edema of the subcutaneous and inter-muscular connective tissue is known as anasarca.

The fluid of edema may be described in general as a clear, usually colorless liquid of low specific gravity, containing a smaller amount of proteids, especially of fibrinogen, than the blood-serum. An inflammatory exudate, on the other hand, is usually turbid, often bloody, of a high specific gravity, and rich in proteids, containing sometimes enough fibrinogen to form fibrin in large quantity.

Formerly the teachings concerning the causation of edema were largely governed by the notion that the transudation occurred through a healthy, unchanged vascular wall, in contradistinction to the inflammatory exudation, which, on account of its more complex composition, was properly regarded as due to grave alterations in the vascular wall. At the present time this distinction between edema and inflammatory exudate, between transudation

and exudation, does not hold good, because there can be no doubt that changes in the walls may play an important part in the formation of certain transudates as well as of exudates.

The formation of the transudates of edema depends principally upon pathologic variations in the blood-pressure, in the composition of the blood, and in the structure and function of the capillary wall.

Experiments have demonstrated that obstruction to the current in the lymph-vessels does not, as a rule, cause edema, on account of the abundant and universal anastomoses, and because the lymph may be reabsorbed by the blood-vessels; total occlusion of all the lymph-vessels of a part may, according to Baldaert, give rise to a pure lymphatic edema, and in the case of increased production of lymph obstruction to the lymph-vessels will hasten the development of edema. Obstruction of the thoracic duct by tumors or other causes usually gives rise to the development of chylous ascites, often preceded by rupture of the receptaculum chyli.

Increased arterial pressure alone does not give rise to edema as long as the venous return is unhindered; but in passive congestion there is an increased transudation from the blood-vessels that often results in the production of edema.

Edema as the result of passive congestion occurs in a widespread almost universal form in cases of general passive hyperemia, such as develops in uncompensated valvular heart disease, in marked cardiac insufficiency from any cause, and as a result of great obstruction to the current through the pulmonary capillaries. In these instances edema usually begins first in the most dependent parts of the body, where the additional influence of gravity causes the greatest increase of the pressure in the veins and capillaries. In general passive congestion the development of dropsy is aided by the fact that on account of the increased intravenous pressure there is some obstruction to the emptying of the large lymph-vessels into the veins at the root of the neck.

Local edema follows local passive hyperemia; thus obstruction to the portal circulation is followed by the development of ascites, except in such occasional instances in which an efficient collateral circulation develops.

The edema is the consequence of the great accumulation of blood in the veins and capillaries, as a result of which the serous fluid is pressed out through the capillary wall into the tissue-spaces to such a degree that the lymphatic circulation, increased to its utmost extent, is not able to remove the excess of transudate. It is reasonable to assume, however, as certain experiments seem to indicate (Emminghaus), that in consequence of long-continued intravascular pressure the permeability of the vessel-wall may be increased. It would seem that under these circumstances the thin, delicate capillary wall could very easily become so altered that liquid would transude more easily than in health. The long-continued distention of the vessels and the consecutive nutritive disturbances may also lead to a loss of elasticity of the extravascular tissues, and this undue laxity would favor the accumulation of lymph.

Increased transudation from the capillaries, with the production of edema, also takes place under a variety of circumstances in which the essential underlying condition seems to be some alteration of the capillary wall. These are the so-called hydremic edemas, which occur more particularly in conditions of chronic infection and nutritive disturbances leading to cachexia. The

edemas now referred to were formerly ascribed to hydremia—*i. e.*, either to an actual increase in the amount of water in the blood, or to a relative increase due to a diminution in the amount of proteids in the serum. But this theory has never been satisfactorily verified by experiment. The injection of large quantities of a 0.6 per cent. solution of salt into the vascular system of animals does not produce edema (Cohnheim and Lichtheim). Even when the blood is replaced to the extent of about one-half its volume by salt solution, so that a marked hypalbuminosis exists, typical edema fails to develop. Still, von Recklinghausen and others hold fast to the hydremic theory. But inasmuch as clinical experience shows that hydremia may exist without dropsy, and that edema may develop without hydremia and without passive congestion, it is quite reasonable to look to anatomic and functional alterations in the capillary walls as the essential causes of certain dropsies.

Hamburger believes that a dropsy of bacterial origin may be produced by bacterial products that circulate in the blood, and either increase the permeability of the capillary wall or stimulate the endothelial cells to an excessive or perverted functional activity. Toxic substances of other origin and the changed composition of the blood in some diseases, such as nephritis, may have similar effects.

Cohnheim and Lichtheim ascribed hydremic edema to a pathologic permeability of the vascular wall. Cohnheim, as well as Thoma, calls attention to one-sided pleuritic effusion, and to unequal amounts of transudation in the two pleural cavities in bilateral hydrothorax (both frequently observed in cases in which the same amount of blood must have been brought to the two pleural membranes under the same general conditions), as pointing directly to a marked difference in the structure and function of the capillary walls in the two sacs. The differences in the case of double hydrothorax may also be due to pressure of the heart itself, particularly the enlarged right auricle, on the return veins.

Heidenhain found that intravascular injection of certain substances, such as the enzymes of the salivary, pancreatic, and gastric secretions, pepsin, egg-albumin, and decoction of the muscles of crabs and crayfish, produced a marked increase in the transudation from the blood—phenomena which he explained as due to the stimulation by these substances of the secreting functions of the endothelial cells.

Recently Loeb has suggested that edema is due to chemical changes, chiefly the result of lack of oxygen, that cause an increase in osmotic pressure in favor of the tissues over the blood and lymph. Pressure thus produced may exceed many times that of obstruction to the circulation.¹

Thoma found that in dead persons arteries and other vessels, the seat of chronic sclerotic changes, were much more permeable to salt solution, injected under a certain pressure, than healthy vessels; and he proposes to call the hydremic edema of cachectic diseases angiosclerotic edema, because there is reason to believe that in a considerable proportion of instances of edema actual vascular disease, or angiosclerosis, is present.

It is a well-known fact that edema is relatively frequent in persons with arteriosclerosis; but the so-called hydremic edema often develops in patients without any arterial or vascular disease in the sense of sclerosis; hence it would perhaps be more in accordance with the actual condition of our

¹ Opitz, *Jour. Am. Med. Assoc.*, Jan. 14, 1899, reviews the development of the theories of edema.

knowledge to refer to this group of edema as angiopathic rather than as angiosclerotic.

The so-called inflammatory edemas probably represent the transition stage between the vascular changes that give rise to pathologic transudation or edema and those that lead to exudation. The fluid of inflammatory edema differs from that of the previous groups in containing more proteids, a larger number of leukocytes, and also fibrinous masses. Inflammatory edema may occur in the vicinity of inflammatory foci, when it is often spoken of as collateral edema; or it may occur as a primary condition, characterized by circumscribed foci of transudation, caused by various toxic, thermic, and traumatic influences, the action of which remains essentially local. Undoubtedly the vascular alterations in these conditions are identical with, or approach very closely, the vascular changes in inflammation that give rise to exudates.

The appearance of edema after spinal paralysis, and the edema of the paralyzed side in hemiplegia, point strongly to the production of an increased permeability of the capillary wall, and excessive transudation or imperfect removal of lymph on account of disturbed vasomotor innervation. Whether so-called neuropathic hyperemias, simple and inflammatory edemas of the skin, as urticaria, erythema nodosum, and angioneurotic edema, as well as those observed in some forms of poisoning and in persons with idiosyncrasy to certain fruits and foods (strawberries, rhubarb, crabs, and shell-fish), are primarily neuropathic or toxic in origin, must be left for future investigators to decide. Wright¹ believes that in some of these conditions a defective coagulability of the blood is produced that leads to transudation. Janowski has shown experimentally that the severing of the vasomotor nerves in conditions associated with edema is followed by marked increase in the transudate.

Transudates in general are colorless or pale yellow, clear fluids, of alkaline reaction, containing a varying amount of proteids, extractives, and salts. A few leukocytes and red blood-corpuscles are also usually present, and in the dropsical accumulations of serous cavities more or less desquamated and degenerated endothelial cells and fat-drops will be found; on rupture of chyle-vessels, chyle may become mixed with the fluid of an existing ascites to such an extent that turbidity results. The milkiness of certain exudates and transudates is, however, not always due to an admixture of chyle, but may depend on a precipitation of albumin.

The composition of transudates is related to that of the blood. Thus, the quantity of proteids and salts in transudates, while always less than that of the blood, corresponds approximately to the amounts of these substances in the plasma (Hoffmann). When the plasma contains certain abnormal substances these may also appear in transudates, as uric acid in nephritis, sugar in diabetes, and biliary coloring-matter in jaundice.

Thoma² gives the following as the specific gravities and percentages of albumin of certain transudates:

	Specific gravity.	Percentage of albumin.
Ascitic fluid in nephritis	1.006	0.56
Ascitic fluid in portal obstruction (cirrhosis of liver)	1.008	0.97
Ascitic fluid in general venous congestion	1.012	1.96
Pleural effusion in nephritis	1.007	
Pleural effusion in general venous congestion	1.012	1.30
Transudates of varying origin	1.007-1.011	0.05-1.1

¹ *Lancet*, ii., 1896.

² *Allg. path. Anat.*

Dropsical organs and tissues present a more or less characteristic water-logged appearance owing to the accumulation of fluid in the tissue-spaces. Tissues containing many spaces may be greatly swollen; an edematous extremity may swell to many times its normal size, due to the dilatation of all the interstices and spaces by fluid, and the skin may be stretched to its utmost. Under pressure of the finger some of the fluid is squeezed aside, and more or less well-marked "pitting" results, which may persist for some time on account of the diminished elasticity of the tissue. Incision of the skin is followed by the outflow of a clear, watery fluid, and reveals the spongy meshes of the subcutaneous tissue filled with transudate. Edema of the lungs is characterized by an increase in volume and great increase in weight; the alveoli are filled with fluid, which on pressure runs freely from the cut surface; if the edema existed before death, so that air was mixed with the fluid, the latter will be frothy. Solid organs, like the kidney, on section show a moist, glistening surface.

Body-cavities the seat of marked and long-continued dropsy usually become dilated, and the serous lining is often grayish and opaque, owing to loosening and degeneration of endothelial cells. Compressible organs, like the lungs, are rendered more compact by the pressure of the fluid (compression-atelectasis).

The transudates gather first in the intercellular spaces, but may also soak into the tissue-elements, producing vacuolation and softening of cells and fibers (Fig. 6).

The consequences of edema *per se* chiefly depend upon its localization. Thus, edema of the folds and structures about the entrance to the larynx (edema of the glottis) may cause rapid death from asphyxia. Edema of the lungs is also often the immediate cause of death. Dropsical accumulations in the peritoneal and pleural cavities may produce such pressure upon the lungs and upon the diaphragm as to interfere seriously with respiration. An acute transudation into the ventricles of the brain and the pia-arachnoid spaces may cause fatal intracranial pressure.

Edema in general is ominous on account of the grave nature of the processes that underly its development.

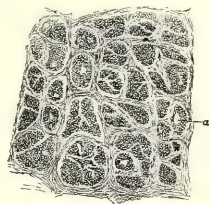


FIG. 6.—Edema of the optic nerve on account of tumor of the cerebellum. At *a* is a vacuole in a nerve-bundle. Weigert's stain. $\times 75$.

THROMBOSIS.¹

Thrombosis is the coagulation of the blood within the heart or blood-vessels during life. The resulting coagulum is known as a thrombus. Masses formed by the adhesion of altered blood-corpuscles and their derivatives are also called thrombi.

The coagulation of blood is a chemical process resulting in the production of fibrin, and it awaits a more simple and satisfactory explanation than it is possible to give at the present time.

The subject is an extremely complex one; it is inseparably connected with the chemistry of the proteids of the blood, and a complete knowledge

¹ For a full and exhaustive consideration of thrombosis and embolism in all their bearings, consult the article by Welch, in Allbutt's *System of Medicine*, vii., 1899.

of coagulation must needs rest upon a better understanding of the nature of these bodies.

Alexander Schmidt,¹ after devoting a lifetime to the study of clotting of the blood, came to the conclusion that the following factors are necessary for the occurrence of the process : 1. Certain soluble proteids, namely, paraglobulin and its derivative, fibrinogen, forming the material from which fibrin is derived. 2. A special ferment, namely, fibrin-ferment, or thrombin, as he calls it, to bring about the necessary changes in the proteids mentioned. 3. A certain amount of neutral salts for the precipitation of the fibrin in an insoluble form.

Arthus and Pages demonstrated conclusively that without the presence of calcium salts fibrin cannot be formed from fibrinogen. They showed that if potassium oxalate is added to freshly drawn blood in such quantity as to precipitate the calcium salts, clotting will be prevented. If a soluble calcium salt is again added, clotting will promptly occur.

In order to explain the relation of the calcium salts to the fibrin-ferment, or thrombin, Pekelherring advances a theory which has been somewhat modified by Lilienfeld, and is based upon the fact that from blood-plasma a nucleo-albumin can be isolated, which, if brought into a solution with fibrinogen and calcium salts, causes a typical clot. The theory is that the so-called "fibrin-ferment" of Schmidt is a compound of nucleo-albumin and calcium, and when it is brought into contact with fibrinogen a reaction takes place, the calcium uniting with parts of the fibrinogen molecule to form an insoluble calcium compound, fibrin. The nucleo-albumin is derived from the leukocytes and blood-plates when they break down and go into solution, and this nucleo-albumin then unites with the calcium salts to form the fibrin-ferment.

Coagulation of the blood depends, then, upon the chemical reaction between fibrinogen of the blood-plasma and the nucleo-albuminate of calcium, in consequence of which an insoluble albuminate of calcium-fibrin is precipitated. Fibrinogen and calcium salts exist in the circulating blood, but the nucleoproteid is derived from the disintegration of the formed elements of the blood, as the leukocytes and the blood-plates. The exact reaction which occurs when fibrin is formed cannot be stated, but it would seem to be quite satisfactorily settled that fibrin is a compound of calcium with a part of the fibrinogen molecule.

It must be assumed that in health thrombosis is prevented from occurring because nucleoproteids are not present in sufficient quantity at any one time. It is true that the necessary elements for fibrin formation are always present, some nucleoproteids being liberated by the constant destruction of blood-corpuscles ; but the smoothness of the endothelial lining prevents the violent disintegration of cells in such numbers that enough nucleo-proteid is liberated at once to cause the precipitation of fibrin ; and probably the small amount of nucleoproteid, or fibrin-ferment, set free under normal conditions is quickly changed or neutralized.

Stagnation of the current favors thrombosis, but does not alone necessarily produce it, because Brücke, Baumgarten, and others found that the blood coagulates with extreme slowness in the lumen of a vessel between two carefully applied aseptic ligatures, continuing fluid for weeks if the vessels are allowed to remain in the living body. A further illustration of the

¹ *Zur Blutlehre*, Leipzig, 1893.

importance of purely physical conditions in the coagulation of the blood is seen in Freund's demonstration that it is possible to maintain the fluidity of the blood for quite a long time by receiving it in sterile glass vessels coated with vaselin, whereas in vessels without any oily coating the blood-corpuscles disintegrate and determine coagulation.

As would be inferred from such observations, thrombosis occurs when the endothelial lining has been roughened or destroyed either by wounds or disease. And yet it is a matter of frequent experience to observe rough and degenerated areas in the endothelium of the vessels, especially of the arteries, without thrombosis. On the other hand, thrombi are found most frequently in those parts of the circulatory system in which the blood-current is liable to become slow and irregular, as in the systemic veins, the recesses connected with the cavities of the heart, in aneurysms, etc. Hence it must be concluded that retardation and irregularities of the current favor thrombosis, not only because of impairment of the nutrition of the endothelium, but also because they seem to be at times associated with or cause changes in the blood-corpuscles that induce the formation of thrombi. According to Freund, the adhesive character of abnormal surfaces is of special importance in causing thrombosis. Irregularities in the current throw the blood-corpuscles more violently against the rough places in the wall, and hence hasten thrombosis in somewhat the same manner as whipping a mass of blood hastens coagulation.

Occasionally instances of unusually rapid and extensive thrombosis are observed that seem to depend upon changes in the general composition of the blood. Such thrombi have been ascribed to so-called ferment-intoxications, and form after extensive injuries, snake-bites, large burns, arsenic poisoning, etc., and in conditions of great general exhaustion. Experimentally it is possible to produce thrombosis by the injection of fluids containing nucleo-albumins; but the fact that thrombosis is somewhat difficult to produce by these methods shows that the body can protect itself within certain limits against coagulation. It is likely that living endothelial cells in some manner restrain coagulation; and Lilienfeld has shown that in connection with leukocytic disintegration a proteid called histon is sometimes formed which has the power to hinder clotting.

Thrombosis may consequently arise under the co-operation of at least three different factors, namely, lesions of the lining of the vessels, irregularities and slowness of the blood-current, and changes in the blood. The two that most frequently enter into the process, and to the direct or indirect concurrence of which the majority of thrombi are attributable, are the lesions of the vascular lining and the disturbances of the blood-current. Zenker has observed that endothelial cells undergoing necrosis present the appearance of a star surrounded by a fibrinous network, showing that the dead endothelium may induce fibrin precipitation, presumably by the formation of the necessary nucleoproteid.

According to their composition, depending upon the relative amount of blood-plates, leukocytes, and red blood-corpuscles, thrombi are usually classified as blood-plate thrombi, and as white, red, and mixed thrombi; between the latter there may be intermediate forms.

The blood-plates (Bizzozero), or hematoblasts (Hayem), are regarded by some as normal constituents of the blood, and by others as the products of the disintegration of white blood-corpuscles (Weigert), or as precipitated globu-

lin (Löwit), or as being formed by the breaking up of red blood-corpuscles (Wlassow, Arnold). Their exact relation to thrombosis has been the subject of much discussion. Bizzozero regarded them as the essential factor in the formation of fibrin, in the sense that they liberated the fibrin-ferment as they underwent destruction; but this conclusion has been questioned by other observers (Weigert, Löwit, Eberth and Schimmelbusch, and others). The so-called blood-plate thrombi have been shown experimentally by Eberth and Schimmelbusch¹ to be formed in conditions of retarded circulation with disturbances of the axial and peripheral currents; if the vessel is compressed or injured chemically with silver nitrate or other agents, a mass of blood-plates will form at the point of injury. At first the individual plates may be recognized, but soon the mass becomes granular or homogeneous. This is the colorless blood-plate thrombus; and upon this may be situated a greater or smaller number of leukocytes. Eberth and Schimmelbusch designate the formation of this thrombus not as coagulation, but as conglutination; and the secondary transformation into a homogeneous or granular, more compact mass, as viscous metamorphosis.

There is much in favor of the theory that the platelet-thrombi are the result of coagulative processes. Löwit, who looks upon the blood-plates as globulin precipitated from the red corpuscles, holds that the plate-thrombus is due to a kind of coagulation, and that the fibrinous substance produced is closely related to the fibrin found in red and mixed thrombi. Arnold and his pupils bring forward strong evidence of a morphologic character to the effect that the separation of platelets from red corpuscles and the formation of fibrinous material from the platelets and other substances derived from the red corpuscles constitute an early and essential step in both intravascular and extravascular coagulation of the blood.

The importance of blood-plate thrombi lies in the fact that they are in all probability the foundation for further and more extensive formations of fibrin and leukocytes that are known as white thrombi.

White thrombi were shown by Zahn to form, like platelet-thrombi, in the marginal zone of the moving stream. In this part of the moving stream red blood-corpuscles are absent. When the wall is injured, or great slowness or gyrations of the current arise, then the marginal zone may become the seat of coagulation. Either a plate-thrombus forms first, fibrin being deposited upon it in successive layers, or a filamentous, fibrinous mass is formed, enclosing blood-plates and white blood-corpuscles. In either case the thrombus, which is coral-like in form, becomes adherent to the vessel-wall, and may grow by apposition of new fibrin until it reaches the axial zone, when red blood-corpuscles become enclosed in the fibrinous network, and the thrombus becomes in part red, in part white—*i. e.*, mixed. From a small beginning, either as a blood-plate thrombus or as a mass of fibrin and leukocytes, the thrombus may grow, by successive deposits of fibrin around its peripheral zone, until it reaches the axial stream and perhaps occludes the vascular lumen. Undoubtedly the majority of the white and mixed thrombi in man originate in the described manner.

The white thrombus is actually gray or yellowish-white in color. Microscopically it consists of minute or coarse threads, that either run irregularly parallel to one another or form a network of granular and hyaline material, and a larger or smaller number of leukocytes and occasional red corpuscles.

¹ *Die Thrombose*, 1888.

The granular and hyaline masses are regarded as due to changes in conglutinated blood-plates, which form a sort of trabecular framework, while the threads are typical fibrin. With time the amount of fibrin increases considerably. The number of leukocytes in the interior of these thrombi is sometimes very great; and as the majority may stain well and appear well preserved, the impression is created that many may have been attracted to the thrombus and wandered into it after it was formed.

Red thrombi occur in stagnating or quiet blood when the conditions are favorable for the precipitation of fibrin. They consist of closely aggregated masses of red cells, separated by delicate or coarse threads of fibrin. Leukocytes are also present.

The mixed thrombus is composed of white and red layers. It may be formed, as already indicated, when a white thrombus gradually extends from its mural attachment out into the current so as to interrupt the axial stream; or it may form by alternating rapid and slow coagulation in larger cavities, as in aneurysms, when the thrombus frequently presents a distinctly laminated appearance. White thrombi may, as they contract, present crevices and cracks into which the blood may pass and clot.

In infective and toxic states capillaries and smaller vessels may be the seat of hyaline thrombi. The hyaline material stains with Weigert's fibrin method, and is regarded by some as derived from red corpuscles, by others as coming from leukocytes.

Thrombosis occurs oftenest in those parts of the circulatory system in which the movement of the blood is subjected to the greatest disturbances, namely, in the systemic veins and in the recesses of the cardiac cavities (the auricular appendages and between the muscular trabeculae of the ventricles). Thrombi are found here in about one-third of those that die from chronic diseases (Birch-Hirschfeld). Wounds, degenerations, and inflammations of the intima of the vessels and of the heart, abrupt dilatations in the course of the vessels, such as aneurysms and varices, narrowing of the vessels from external compression, are all conditions favorable for the development of thrombosis.

Wounds of the blood-vessels usually lead to the conglutination of blood-plates along the margins, and this may be followed by the growth of a white thrombus, the whole being a process which may be of material aid in the immediate closure of the opening.

Ligation of a vessel leads to arrest of the current up to the nearest collateral branch. Baumgarten has shown that a carefully tied ligature need not be followed by thrombosis; but if the intima is ruptured by the unnecessary tightening of the ligature a small thrombus forms along the circular tear. If the vessel is the seat of sclerotic changes with defects in the endothelium, or if acute suppurative inflammation develops, then a red thrombus is sure to form up to or beyond the nearest branch. If the ligature now "cuts through" the wall—*i. e.*, if union between the opposed surfaces fails to occur—the thrombus is the only guard against hemorrhage; it may give way readily, and this would be followed by the dreaded secondary hemorrhage of the preaseptic era.

In the heart the various forms of acute endocarditis are nearly always associated with thrombic deposits upon the necrotic and changed areas, helping to form the vegetations characteristic of endocardial inflammation. Thrombi that originate primarily in the auricular appendages or in the

recesses between the muscular trabeculae of the ventricles may grow by apposition to form larger masses that formerly were designated as cardiac polypi. Occasionally such polypoid masses become loosened, and if they are too large to pass the auriculoventricular openings, they remain in the auricles as free "ball-thrombi."

In the arteries white or mixed thrombi may develop upon roughened places in the intima and project as *parietal* or *mural* thrombi into the lumen of the vessel (Fig. 7). In a smaller vessel such parietal formations

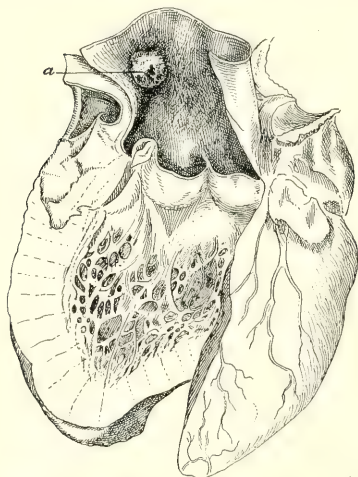


FIG. 7.—a, Parietal thrombus upon a rough (atheromatous) spot in the intima of the aorta.

may grow by apposition until the lumen becomes completely closed, when the thrombus is spoken of as *occluding*. Such original or *primary* (autochthonous) thrombi may give rise to *secondary* thrombic deposits, that grow chiefly in the direction of the blood-current and extend as far as the nearest branch, and sometimes farther; such secondary, propagated, or induced thrombi are usually red, due to coagulation in the blood-mass.

The dilatations or aneurysms that develop in connection with arteries are frequently the seat of extensive thrombosis—dilatation-thrombi—because of the roughness of the intima and the whirls and eddies made by the blood-current in their interior.

In the veins varicosities, as well as interferences with the venous circulation in general, may give rise to small white thrombi in the pockets formed by the valves; these primary thrombi may grow by surface deposition until they occlude the lumen and give rise to a propagated red thrombus reaching to the next branch. Here the projecting blunt end of the thrombus may become capped by white or mixed deposits until the lumen is once more closed; a new red thrombus again forms, and this process may repeat itself until the small primary thrombus behind the valve of a vein—in the leg, for instance—may have given rise to thrombosis far up into the vena cava.

Suppuration and necrosis in the vicinity of veins or arteries which extend so as to involve the vascular wall, or inflammation and necrosis due to the implantation upon the intima of micro-organisms circulating in the blood, or to the action of toxic substances, also frequently give rise to thrombosis; and in this case the thrombus is often invaded by bacteria (suppurative thrombophlebitis or thrombo-arteritis). Thrombosis of the smallest vessels is frequently caused by infectious or toxic inflammations and necrosis in the tissues around them (Fig. 8).

The general states especially favorable to the development of thrombosis

are those marked by great prostration and cardiac feebleness. Thrombi developing under these conditions are commonly called *marantic* thrombi, according to Virchow, who regarded the marasmus as the underlying factor.

Thrombi of this class are found in the pockets of the valves, in the auricular appendices, in the recesses between the muscular trabeculae of the cavities of the heart, but most frequently in the sinuses of the dura mater and in the femoral veins; here extensive thrombosis may take place. The general weakness of the heart, the slowness of the circulation, and the vitiated condition of the blood in marasmus all favor local degeneration of the endothelium. In many instances of marantic thrombosis it is difficult to exclude entirely the influences of accidental or terminal infections.

The extensive thrombosis that at times follows injection of extract of thymus gland, and the transfusion of blood from one animal into one of another species, sublimate and arsenic poisoning, and many general infections, makes it probable that chemical substances may gain entrance to the circulation and determine thrombosis by their direct action upon the constituents of the blood (ferment-thrombosis).

Disturbances of the circulation and changes in the vessel-walls determine the localization of thrombi; while changes in the chemistry and morphology of the blood are important predisposing causes (Welch).

The principal causes of thrombus formation may, following Birch-Hirschfeld, be summarized in this way:

1. *Thrombosis from adhesion*: *a*. On foreign bodies; *b*. On the inner surfaces of vessels the seat of necrosis, fatty degeneration, or inflammation.

2. *Thrombosis from stagnation*: *a*. From local disturbance from ligation, compression, circumscribed dilatation; *b*. From general circulatory weakness (marantic thrombosis).

3. *Thrombosis from fermentation*: *a*. Due to destruction of blood-corpuscles; *b*. Due to the introduction of ferments formed outside of the vessels.

The immediate consequences of thrombosis depend upon the character of the thrombus, whether it is parietal or occluding, and upon the vessel involved, whether that is provided with collateral branches or not. An occluding venous thrombus causes passive congestion and increased transudation in case collateral circulation does not develop, as, for instance, in the portal vein. An occluding arterial thrombus has, in general, the same effects as embolic arterial occlusion.

The more indirect results of thrombosis are connected with the secondary changes that take place in thrombi. A thrombus retains its original structure for a very brief time only. The changes that occur may be separated into five principal kinds: hyaline and granular transformation, substitution with connective tissue, calcification, simple softening, and septic disintegration.

It must be mentioned that a fresh or recent thrombus may be detached, either in part or as a whole, and carried farther in the current as an embolus



FIG. 8.—Small tubercle with giant cell in the wall of a pial vein in tuberculous meningitis, covered with a hyaline granular thrombus containing many leukocytes. Alcohol, paraffin, hematoxylin, and eosin. $\times 150$.

until it becomes impacted in some vessel the lumen of which is too small to allow its passage. The farther changes of such an embolus are essentially the same as would have occurred if it had remained as a thrombus at its place of formation.

The hyaline-granular transformation begins with a contraction of the fibrin in the thrombus, which squeezes out the fluid in its interior and reduces its size. The fibrin and red and white cells undergo disintegration into a granular mass, which later may become homogeneous. The columns of platelets are recognized with difficulty. The hemoglobin is transformed into various pigments, and is in part removed. Gradually the mass shrinks still more, becomes quite dry and rather firm. This contraction of the thrombus may reopen the lumen in case it was occluded. Such a hard, hyaline and granular thrombus may now be gradually replaced by connective tissue. In this process the thrombus, which must be regarded as an absolutely dead mass, does not take an active part. The new connective tissue comes entirely from the vessel-wall. In the interior of the thrombus leukocytes appear that have wandered in from the blood, and act as phagocytes. Beginning at its points of attachment to the wall, a layer of endothelial cells gradually spreads over its surface. Simultaneously new capillaries spring from the vasa vasorum and enter the thrombus. The endothelium on the surface of the thrombus also forms vascular spaces. New connective tissue develops around the capillary loops. This connective tissue comes from proliferation of cells in the wall of the vessel (or heart). The capillaries from the vasa vasorum unite to a certain extent with the spaces formed by the endothelial cells; the thrombus is now vascularized, and communication may be established with the lumen of the vessel. Gradually the thrombus becomes smaller, due to contraction of the newly formed connective tissue and to absorption of the dead material. Finally the absorption may be complete and the contraction so extreme that merely a narrow strand of fibrous tissue marks the site of the former clot, and the blood-current passes unhindered; or there may remain more or less distortion or narrowing of the lumen and thickening of the wall. In unfavorable instances, especially when the thrombus remains attached for some part of its extent to the entire circumference of the vessel, the latter may become converted into a fibrous cord without any lumen whatever in its interior.

For various reasons a thrombus may fail to become replaced by connective tissue. Disease of the vessel-wall and infection may prevent or delay the process. In the old the changes require a longer time than in the young.

Thrombi may become impregnated with the salts of lime and calcify. This may occur in thrombi upon the valves of the heart as well as in those in the interior of vessels. The concretions formed are spoken of as phleboliths in the case of veins, and as arterioliths in the case of arteries. Phleboliths are the more common, and are found quite often in the venous plexuses in the pelvis.

While connective-tissue substitution and calcification are favorable terminations of thrombosis, the forms of softening that occur in thrombi are connected with grave dangers.

Simple, or bland, softening is the result of obscure chemical or fermentative changes in the interior of the thrombus without the presence

of bacteria. The center is gradually changed into a soft, reddish-gray or grayish detritus; if the softening extends to the superficial layers of the thrombus, then the particles and fragments may be discharged into the circulation and give rise to embolism.

Septic, or purulent, softening of a thrombus is due to the presence of micro-organisms, and occurs especially when the thrombus develops in connection with suppurative phlebitis or arteritis, although infection may occur in a thrombus formed upon sterile walls. There is an accumulation of polynuclear leukocytes, and the thrombus is changed into a yellowish, purulent fluid, which may become putrid and foul. If the infected material is transported by the current to distant places, secondary foci of suppuration and the condition known as pyemia may develop.

After death the blood recedes to the capillaries, the veins, and the heart by the retraction of the arteries. Probably because in contact with endothelium it remains liquid for some little time, but within a few hours it clots. When this coagulation is rapid the coagula are dark red. If it is slow, variations in color may appear. The red blood-corpuscles, being specifically heavier, sink before coagulation begins, and the uppermost plas-matic layers form yellow fibrinous clots (chicken-fat clots) which are moist and gelatinous, while the lower strata consist of deep-red masses (currant-jelly clots). The agonal and postmortem clots are not stratified; they are moist and gelatinous, not granular; and they are not intimately attached to the vessel-wall or heart-wall, although they may be infiltrated between the muscular trabeculæ of the cavities of the heart.

EMBOLISM.

Our knowledge of embolism rests essentially upon the anatomic and experimental investigations and teachings of Virchow.¹

Embolism is the impaction in some part of the vascular system of any undissolved material brought there by the blood-current (Welch). The material transported in this manner is an *embolus*.

A systematic consideration of embolism necessitates a brief account of the origin and nature of the various kinds of emboli, of the routes of transportation and the manner of lodgement, and of the mechanic as well as the specific results of embolism.

Emboli may consist of:

1. Thrombi or pieces thereof, tissue-fragments, and various kinds of parenchymatous cells.

Many emboli consist of thrombic masses. Either a whole thrombus is loosened from its place of origin or a portion projecting into the blood-current is broken off, or fragments are carried away by the circulation from thrombi that are undergoing either simple or septic softening.

The favorite seats of thrombi that give rise to embolism are upon the endocardium, in the veins of the lower extremities and of the broad ligaments, and in the aorta when the intima is rough and irregular from chronic disease; but thrombi in any part of the circulatory system may become the source of emboli.

Fat-drops constitute the most frequent form of emboli. Fractures with destruction of the bone-marrow, contusions of the subcutaneous adipose

¹ *Gesammelte Abhand.*, 1856.

tissue, acute as well as chronic osteomyelitis, injury to fat-tissue in any part, such as lacerations of the liver, fatty changes in thrombi and in the vascular lining, are all conditions that may be followed by fat-embolism (Fig. 9).

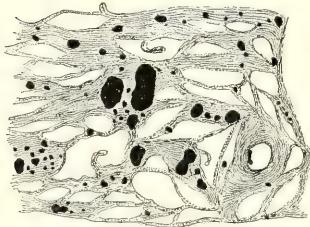


FIG. 9.—Fat-embolism of the lung after fracture of the femur. The fat-globules and masses, stained black with osmic acid, lie in the capillaries of the lung. $\times 150$.

A limited fat-embolism occurs, in all probability, in most fractures, but only occasionally are the results so serious as to attract attention. It also may follow orthopedic interventions. In all these instances the injury, or the disease, causes a disintegration of the cells containing the fat, which then finds its way in larger and smaller drops and masses into the patent lumen of torn veins; occasionally single fat-cells or islands of them may be carried away.

In diseases of the endocardium and of the intima of the blood-vessels degenerated endothelial cells, fragments of the heart-valves, inflammatory vegetations, and calcareous masses may be carried off by the blood-current.

Liver-cells, placental cells, giant cells from bone-marrow, and other parenchymatous cells may form emboli. Embolism from liver-cells (Turner, Schmorl, and others) may follow rupture, acute degeneration, and hemorrhages in the liver. Embolism of placental giant cells (syncytium) and of chorionic villi occurs especially in puerperal eclampsia; but also in normal labor. After injury to bones, in various toxic and infectious conditions, and in leukemia the giant cells of the bone-marrow frequently lodge as emboli in the pulmonary capillaries (Lubarsch, Aschoff, and others). Splenic cells (Welch) and fragments of the myocardium (Charrin and Levaditi) are other examples of cellular emboli. For references to the literature bearing upon embolism of parenchymatous cells, see Lubarsch and Ostertag's *Ergebnisse*.

In most cases cellular emboli undergo retrogressive changes and disappear. It is possible that emboli of apparently normal syncytium may give rise to tumor-growth (Schmorl). Thrombi may form around cellular emboli; this is especially so in regard to liver-cells.

2. Tumor-cells. Emboli composed of living cells, capable of farther proliferation, occur in connection with malignant tumors. In carcinoma and sarcoma isolated tumor-cells or cell-groups may reach the blood-current either indirectly through the lymphatics, or directly when the tumor in its growth penetrates the wall and projects into the lumen of a blood-vessel. On lodgment the cells proliferate and give rise to secondary tumors (Fig. 10).

3. Animal and vegetable parasites.

Bacteria of various kinds, as well as protozoa and the embryos of a few large animal parasites, may be transported by the circulation and act as emboli.

4. Foreign bodies; air.

Foreign bodies rarely, if ever, get into the circulation and act as emboli, except when introduced for experimental purposes; but atmospheric air gives rise to embolism by gaining entrance into veins opened accidentally or during surgical operations. The danger of air-embolism is especially

great when large veins near the thorax are opened, into which the air may be directly aspirated by the negative venous pressure during inspiration.¹

As a general rule, emboli follow the direction of the blood-current. The extent of their travels is largely dependent upon their size. Lodgement takes place in the nearest vessel, the lumen of which is too small to allow the embolus to pass; more rarely an embolus is arrested at an arterial bifurcation.

As the majority of large emboli originate from thrombi in large veins, their natural course is through the right heart and into the branches of the pulmonary artery; emboli originating in the right auricle or ventricle also pass into the pulmonary artery. Here the embolus lodges at some point of narrowing of the artery, usually at a bifurcation, producing closure of the lumen of one or both branches. A friable embolus, composed of an old thrombic mass, may break into many fragments as it strikes the point of the arterial bifurcation; multiple embolism of the smaller branches may thus result. Occasionally the main stem of the pulmonary artery, or its large branches, are completely blocked by an embolus originating in a peripheral vein the seat of an extensive thrombosis. The blocking of the pulmonary artery depends upon the embolus having been rolled together into a large clump by the blood-current; when disentangled by gently moving the embolus to and fro in water, a complete cast of the lumen of the venous network whence it came may be obtained.

Emboli originating in the pulmonary veins, the left ventricle and the left auricle, and the aorta are carried along the arterial current into the more or less distal ramifications of the aorta.

Emboli arising in the radicles of the portal vein lodge in the hepatic branches of this vein—*i. e.*, in the liver.

There are two exceptions to the general statement that emboli follow the normal direction of the blood-current, namely, the case of *paradoxical* or *crossed* embolism, and the case of *retrograde* embolism.

Paradoxical, or crossed, embolism was first described by Cohnheim. It occurs when defects in the interauricular or interventricular wall of the heart, as, for instance, a patent foramen ovale or a congenital defect in the ventricular septum, allow emboli originating in the systemic veins to pass directly from the right chambers of the heart into the left, and to lodge in the systemic arteries instead of in the pulmonary. The frequency with which a patent foramen ovale is seen suggests that crossed embolism is more common than is generally supposed. In cases of obscure systemic embolism this route should be carefully examined. Paradoxical embolism may also take place through the patent ductus arteriosus.

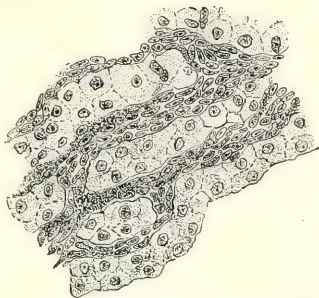


FIG. 10.—Embolism of pigmented sarcoma-cells into capillaries of the liver. The intrahepatic capillaries are filled to distention with spindle-shaped cells containing brown, granular pigment. The liver was uniformly brownish-black, and enlarged to many times its normal size on account of this diffuse infiltration with tumor-cells. The primary tumor was a melanosisarcoma of the eye. Müller's fluid, celloidin, hematoxylin, and eosin. $\times 2500$.

¹ N. Senn, *Experimental Surgery*, 1888.

Retrograde embolism (Heller,¹ von Recklinghausen²) takes place when an embolus is transported in a direction opposite to that of the normal current. As far as we know, retrograde embolism occurs only in the veins; thus, for instance, an embolus may be carried from the ascending vena cava into the renal vein or into the hepatic vein. Cases are described in which tumor-masses and parenchymatous cell-emboli have travelled in a backward direction in the veins. Retrograde embolism is usually explained as caused by sudden reversals in the venous current on account of obstruction to the emptying of the veins into the right auricle, such as great respiratory efforts, etc. Ribbert,³ however, concludes that the emboli which seem to adhere or lie in apposition to the vessel-walls are forced backward slightly with each pulse-beat.

Embolism also occurs in the lymph-vessels; an apparently backward embolism is more frequent here than in the veins, as shown, for instance, by the formation of secondary carcinomatous growths in lymph-glands located behind or distal to primary tumors. Waldeyer and Cohnheim thought the tumor-cells might go in this direction by their own movement. Heller and Vierth⁴ conclude that as lymph-glands become occluded the stream, which is normally very slow, may become reversed; dilatation of the vessels, leading to incompetency of the valves, results, and now backward embolism can easily take place.

Minute foreign masses that can pass through capillary networks are sometimes called capillary emboli; they do not remain indefinitely in the circulatory system, but become deposited in various organs. Arnold found that small foreign bodies in the blood became surrounded and isolated by leukocytes. Numerous experiments by Ponfick and others with granular coloring-matter have shown that it is deposited either free or within cells in various organs, especially the liver, spleen, bone-marrow, and tonsils.

The Effects of Embolism.—The effects of embolism are, generally speaking, twofold: a mechanic, depending upon vascular occlusion at the point of lodgement; and specific, depending upon the nature of the embolus, whether infected or sterile, whether composed of dead cells or of living cells capable of further proliferation.

In some instances embolism is followed by sudden death: thus, the closure of the pulmonary artery or its two branches by large embolic masses results in almost instantaneous death; embolic occlusion of the bulbar arteries and of the coronary arteries may cause sudden death.

A moderate amount of fat-embolism can occur without serious consequences; in such cases the fat is gradually saponified and removed by wandering cells. When a large quantity of fat is taken into the circulation it may accumulate in the pulmonary capillaries (Fig. 9); some of it may pass through and lodge in the capillaries of the myocardium and brain, and in the glomerular and intertubular capillaries of the kidneys. Under these circumstances death may occur.

Air-embolism may cause sudden death. When large quantities of air are taken into the circulation, the branches of the pulmonary arteries are filled with bubbles; at the same time there is formed in the heart a frothy mass of blood mixed with air, which is resilient, so that the contractions of the heart are unable to drive it onward. In consequence the left heart

¹ *Arch. für klin. Med.*, viii., 1870.

³ *Centrab. für allg. Path. u. path. Anat.*, viii., 1897.

² *Virchow's Archiv*, c., 1885.

⁴ *Ziegler's Beiträge*, xviii., 1895.

receives but little blood, the aortic pressure falls, and death results. Air-bubbles may also find their way into the capillaries of the systemic circulation and occlude important capillary areas in the brain and in the heart-muscle. The discovery by Welch and Nuttall¹ of *Bacillus capsulatus aërogenes*, which causes an abundant and rapid development of gas in the blood after death, makes it not improbable that some cases of supposed air-embolism were in reality of bacterial nature. Great care must be exercised in the interpretation of obscure instances of death under circumstances that simulate air-embolism, especially when of uterine origin. Experiments show that a much greater quantity of air is necessary to kill animals than can possibly be introduced during an operation. Man, however, seems more susceptible than the dog or the horse.

The changes in the embolus itself after it has become wedged in a vessel depend upon its nature. If composed of sterile thrombic masses, the further changes are those that occur in a sterile thrombus in any part of the circulation. Immediately after the lodgement some new deposits of fibrin may take place upon the surface of the embolus, and the secondary thrombosis may complete the obstruction of the vessel. At the point of impaction necrosis of the endothelium may occur from pressure, followed by connective-tissue proliferation from the vessel-wall and replacement of the mass with granulation-tissue. Occasionally connective-tissue substitution of an embolus leads to obliteration of the lumen of the vessel; at other times the intima presents as a result irregular thickenings or perhaps a more or less elaborate network of connective-tissue threads.

It has been suggested by some that the embolic lodgement of calcareous particles may result in aneurysm and rupture of the vessel in which the embolus lodges.

Emboli composed of aseptic material are called bland, and their effects are only of a mechanical nature, and due primarily to the plugging of the vascular lumen (Fig. 11). As a general rule, occlusion of an artery leads to the development of a collateral circulation, which provides the area nourished by the plugged vessel with sufficient blood-supply. In certain parts of the body, however, the facilities for the development of a collateral circula-

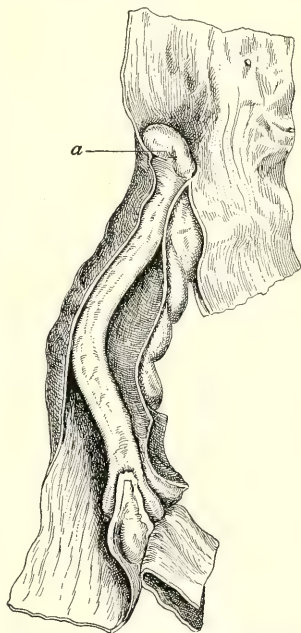


FIG. 11.—At *a* a large embolus is lodged at the beginning of the right common iliac artery, which is occluded by a secondary thrombus, causing gangrene of the corresponding extremity and necessitating amputation. The embolus was a clot from a heart-valve the seat of extensive inflammation.

¹ *Johns Hopkins Hosp. Bull.*, iii., 1892.

tion are either entirely absent or so limited that arterial occlusion is followed by death of the tissue before a collateral circulation has time to develop (page 46). Embolic occlusion of a terminal artery renders the area supplied by that artery primarily anemic. In the spleen, the kidneys, the myocardium, the retina, and the basal ganglia of the brain, arterial occlusion is regularly followed by death of the tissue affected. In the superior mesenteric artery and the pulmonary arteries occlusion, embolic or otherwise, is often followed by necrosis. The further fate of the anemic areas and the special conditions presented after arterial occlusion in various organs provided with end-arteries have been dwelt upon in connection with local anemia and necrosis.

Bland embolism of the branches of the portal vein in the liver is generally without result on account of the additional circulation in this organ provided by the hepatic artery, which normally is abundantly able to maintain the nutrition. When the flow in the hepatic artery is feeble, plugging of the portal branches produces wedge-shaped areas of a reddish color.¹

Peculiarities of embolism of other special vessels are discussed in sections on pathologic anatomy.

Retrograde bland embolism of veins without collateral circulation, such as the splenic and renal veins, causes obstruction to the venous current, extensive passive congestion with perhaps complete stasis, and hemorrhagic infiltration in the areas drained by the occluded veins.

Emboli composed of or containing virulent pathogenic bacteria, animal parasites, or living tumor-cells, may produce on lodgement the same mechanic effects as bland emboli; but these effects usually remain in the background, because the consecutive tissue-changes and new foci of disease caused by the infected and specific emboli are of much greater importance.

Bland capillary emboli are ordinarily of but little consequence, except when in great number; but capillary emboli of virulent bacteria and of tumor-cells are as important as larger emboli, for the reason that when implanted upon the capillary wall of some internal organ, such as the liver, the spleen, the bone-marrow, or the lungs, they give rise to new foci of morbid processes. Thus, for instance, in acute ulcerative endocarditis bits of vegetations and disintegrated tissue containing bacteria may be carried as emboli to the various parts of the systemic circulation, where the bacteria may proliferate and cause multiple abscesses and areas of necrosis. A vein the seat of a suppurative inflammation in its wall, accompanied by thrombosis, may become the source of multiple emboli, large as well as capillary, which, lodging in the lungs and elsewhere, give rise to multiple secondary abscesses. The destructive action of bacteria in emboli may cause such weakening of the vessel-wall at the point of arrest of the embolus that aneurysms develop (embolic or mycotic aneurysms).

Emboli of tumor-cells give rise to multiple secondary tumors in various parts of the body, especially in the lungs and the liver (Fig. 10). In these cases the secondary foci of disease invariably correspond in their kind with the primary focus in which the embolus took its origin.

Secondary embolic foci of suppuration and of malignant tumors are also called *metastatic*; the transplantation by embolism of suppurative infection, as in pyemia, and of malignant neoplasms is known as metastasis.

¹ Chiari, *Centralb. für allg. Path. u. path. Anat.*, ix., 1898.

THE RETROGRESSIVE METAMORPHOSES.

Introduction.—Cellular life and activity are manifested by nutrition, by reproduction, and by function (Virchow). Nutrition is shown by the growth of the cell-body and by the secretion of intercellular substance. Reproduction manifests itself in the phenomena of cell-multiplication. The function of the cell is the office it fills in the service of the organism as a whole.

Nutrition, reproduction, and function are the result of metabolic processes in the cell which transform the energy stored in food into other forms of energy.

As a consequence of disturbances in the activity of the cells there result, on the one hand, different varieties of disintegration and shrinking of the tissues—retrogressive changes; and on the other hand, abnormal forms of growth and proliferation—progressive changes.

The retrogressive changes or metamorphoses depend upon various causes that may operate in different ways. The life of the cell may be directly destroyed by certain agencies, or various degrees of disturbance in the conditions that are requisite for cellular activity and life may arise. In all cases the final result may be the same—namely, cellular death.

When the death of a cell or group of cells occurs directly and rapidly, without the previous intervention of abnormal alterations in the cellular structure, the term *necrosis* is applied. When death of the cell is preceded by a gradual shrinking in size (atrophy), or by demonstrable alterations in structure, due either to abnormal chemical processes in its interior (degeneration), or to the deposition in its protoplasm of foreign substances from without (infiltration), the condition is spoken of as *neurobrosis*.

While the logical distinction between these two general forms of cell-death is easy, it is not always practically possible to distinguish between them on the basis of chemical changes and morphologic appearances. Generally speaking, however, the retrogressive changes that lead to neurobrosis occur so gradually, and present in many instances such definite forms and characteristics, that they are, as a rule, accorded a separate consideration.

As already indicated, under certain circumstances the general environment of the cells is unfavorable in such a way that the consequent imperfect cellular nutrition leads to a progressive shrinking of the individual cells, and this shrinking is designated as atrophy; and neurobrosis is often the further result of atrophy. When abnormal intracellular metabolism converts the cell-protoplasm directly or indirectly into useless and abnormal substances the process is known as *degeneration*, which becomes a neurobiotic change when it leads to the destruction of cells. According to the nature of the substances produced, various forms of degeneration have been established, such as fatty, mucoid, hyaline, etc. When substances produced within the body or introduced into the organism from without are deposited in the interior of cells, which remain essentially passive, or in dead material, *infiltration* is said to occur. Infiltration may reduce the vitality of the cells and thus favor cell-death.

NECROSIS.

Necrosis is the death of individual cells or groups of cells while they are still a part of the living body. Local death preceded by retrogressive changes

in the cells, such as occur in atrophy, in degenerations, and in infiltrations, sometimes receives the special designation of necrobiosis.

The real nature and essence of necrosis cannot be expressed in words, since it is not known what constitutes the life of the cell. No one has seen under the microscope, or isolated chemically, the particular detail or substance of the living cell that disappears or changes at the moment of death, and the disappearance or change of which constitutes death of the cell. All those peculiar appearances which indicate that a group of cells was dead while still in the living body or before the surrounding cells died are chiefly postnecrotic or postmortem changes. By means of modern fixing solutions, such as corrosive-sublimate solution, Flemming's solution, absolute alcohol, etc., it is now possible definitely to fix and preserve in the cells the histologic appearances that are present at the moment the tissue is placed in the fluids. Our notions concerning the structure of the normal living cell have largely been gained by studying cells killed in this way.

In necrotic cells the nucleus very soon becomes indistinct, due either to an apparent solution of the chromatic substance, known as *karyolysis* or *chromatolysis*, or to a breaking up of the nucleus into a number of irregular fragments, a form of disintegration which Klebs¹ called *karyorhexis*, and which Schmaus and Albrecht² have shown is initiated by a peculiar transposition of the chromatic filaments. At times the nucleus together with the cell-body changes into a hyaline mass. The cytoplasm of necrotic cells loses its normal granulations and undergoes hyaline transformation, or vacuolation. The exact chemical processes that underlie these changes in necrosis are not known. In many instances the factors necessary for the precipitation of fibrin are present, giving rise to the so-called *coagulation-necrosis*.

The postnecrotic changes vary greatly according to the different conditions surrounding the necrotic part. They serve not only as an evidence that necrosis has occurred, but also, in part at least, as a basis for the classification of the necroses. The secondary vital changes, such as leukocytic emigration and proliferation of the fixed cells occurring about the foci, help to differentiate true necrosis from focal changes that may occur after the death of the organism as a whole.

Necrosis may result from the direct action upon the cells of chemical and toxic substances of various kinds; mechanic insults may also cause direct cell-death; anemia, in consequence of arterial occlusion by thrombosis, embolism, spastic contraction, and compression, is a frequent and important cause of necrosis; complete stasis due to mechanic, chemical, thermal, and trophic injuries of the vessel-wall is likewise often a factor in cell-death. And, finally, disturbances of the trophic and vasomotor innervation may, especially when associated with other causes, produce necrosis. In many instances these agents bring about necrosis at the point of greatest or longest contact; whereas at the periphery more complex reactive tissue and vascular changes are initiated, which are further discussed under Inflammation.

The etiologic and anatomic varieties of necrosis, although not always sharply distinguishable from one another, are best considered under the following subdivisions:

Focal Necrosis.—Focal necrosis occurs in various organs of the body in the course of different infections and intoxications, and is caused by the

¹ *Die krankhaften Störungen des menschlichen Körpers*, 1889.

² *Virchow's Archiv*, 138, Supplement Heft.

circulation in the blood of either living bacteria or of soluble poisons that act more or less directly upon the cells, often without preceding circulatory disorder. In such conditions we find scattered throughout the lymph-glands and parenchymatous organs foci of cell-death, usually microscopic, characterized by certain well-marked changes, of which the most striking affect the nucleus.

Very frequently, perhaps in the majority of cases, the nucleus undergoes fragmentation (karyorhexis, Klebs)—*i. e.*, the chromatin disintegrates into a number of particles and granules, which are scattered about through the focus before they gradually vanish. In other cases the nucleus loses its power of staining with the various nuclear dyes, because the chromatin has been dissolved (karyolysis). At the same time the cell-body becomes homogeneous and opaque, or hyaline, and soon the outlines become completely lost in the granular detritus or the more reticulated material that finally forms. The necrotic material often resembles fibrin.

Attracted by certain substances in the necrotic areas (positive chemotaxis), leukocytes accumulate at the periphery; some of these in turn also die, and suffer nuclear fragmentation and other changes, so that often large quantities of nuclear detritus collect around the areas of cell-death. Later, the necrotic material and detritus become absorbed; regeneration of the dead cells may, in the case of smaller foci, take place by multiplication of the surrounding cells, or the necrotic area may be replaced by newly formed connective-tissue.

Such focal, or insular, necrosis is seen in the lymph-glands, the liver, the spleen, and elsewhere, and was first observed by Oertel in diphtheria. It occurs in experimental diphtheria after subcutaneous injection of virulent cultures of diphtheria-bacilli, and after the injection of the toxins produced by the diphtheria-bacillus (Welch and Flexner).

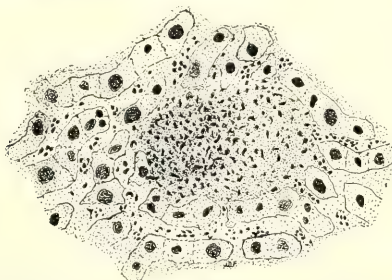


FIG. 12.—Focal necrosis in the liver in puerperal eclampsia. Nuclear fragments are strewn over the necrotic area. $\times 250$.

It is also of common occurrence in typhoid fever. The so-called lymphoid nodules of this disease in the liver and kidneys have recently been shown by Reed¹ to be areas of necrosis; but he was not able to determine whether they were due to the immediate presence of the typhoid bacilli or to the action of the toxins. According to Mallory,² the degeneration of the intravascular phagocytic cells in typhoid fever induces the for-

¹ *Am. Jour. Med. Sci.*, 1895.

² *Jour. Exper. Med.*, iii., 1898.

mation of fibrin, which leads to necrosis. Similar changes occur in scarlet fever (Pearce).

Localized areas of cell-death occur in the liver in puerperal eclampsia (Fig. 12), and also in the spleen, the liver, and the adrenals, in general tuberculosis (Fig. 13) associated with marasmus, in which they have been shown by Le Cout¹ to be due, in all probability, to the immediate presence of tubercle-bacilli, and not to primary vascular changes.

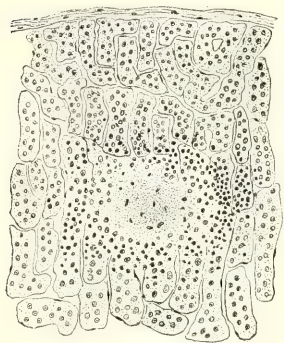


FIG. 13.—Focal necrosis in the adrenal in chronic pulmonary tuberculosis. Leukocytes are accumulating around the area. $\times 150$.

Focal necrosis in the various organs is regularly produced to a marked extent in experimental intoxication with ricin and abrin, toxalbumins of vegetable origin, and with the toxic substances contained in the serum of the dog's blood (Flexner).² The toxemia of burns also causes areas of necrosis in the organs (Bardeen).

Regarding the causation of focal necrosis in the various conditions mentioned, it would appear that it either results in consequence of the direct action of bacteria, or perhaps more frequently is caused by certain soluble substances, generally known as toxalbumins.

When such soluble toxic substances gain entrance into the circulation, as from a point of local infection, they may, on account of the momentary arrest of the circulation in a capillary, find an opportunity to produce necrotic changes in the capillary wall. Through this altered wall a free transudation of serum takes place, and leads to the death of cells. In other instances the necrosis may result from capillary thrombosis. Necroses may also be produced during the process of elimination or destruction of bacteria or their products by various organs.

The exact genesis of focal necrosis and the further fate of the affected areas are of great interest. It is not unlikely that necroses of this character bear an essential relationship to the production of the connective-tissue overgrowth in certain diseases, as chronic interstitial nephritis and cirrhosis of the liver.

Fat-necrosis.—Fat-necrosis occurs in adipose tissue in the form of yellowish-white, slightly raised, opaque areas of variable size, and usually of more or less circular outline (Fig. 14). Microscopically the contents of the fat-cells are changed into a granular detritus (Fig. 15) or present the appearance of fine needles radiating from the center, while the cells proper undergo necrosis. If the tissue is treated with osmic-acid solution, the surrounding fat-cells stain black, while the necrotic areas remain unchanged.

Langerhans has shown that the detritus in the fat-cells consists of a combination of lime salts with fatty acids.

Fat-necrosis occurs frequently in the abdominal fat in connection with inflammatory conditions of the pancreas. Balser, who first described it, believed that it was due to an overgrowth of fatty tissue, parts becoming

¹ *Jour. Exper. Med.*, ii., 1897.

² *Johns Hopkins Hosp. Rep.*, vi., 1897.

necrotic from lack of nourishment, and held that the pancreatic disease was secondary. Fitz,¹ while concluding from his researches concerning acute pancreatitis that fat-necrosis may occur without any direct relation to pancreatic disease, thought that it often develops secondarily to acute pancreatitis.

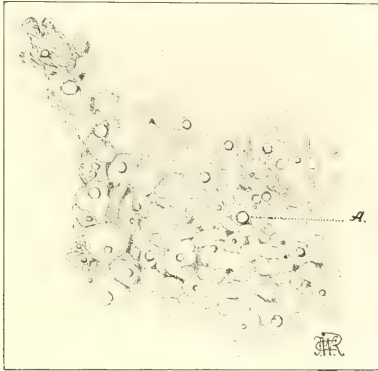


FIG. 14.—Section of omentum with areas of fat-necrosis scattered through it (A). From a case of acute pancreatitis.

It has not been shown that bacterial infection is the cause of this necrotic change in fat, although Ponfick claimed to have found a bacillus in the diseased areas.

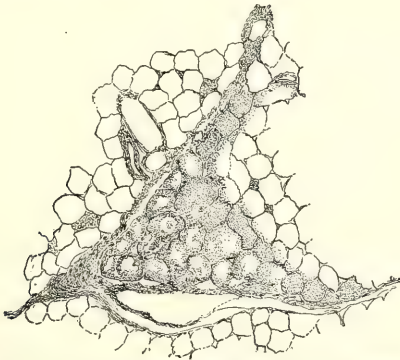


FIG. 15.—Fat-necrosis in the omentum in acute pancreatitis. $\times 76$. The contents of the fat-cells are changed into a granular detritus.

The most plausible theory concerning the cause of fat-necrosis is that it is due to the escape of the fat-splitting ferment of the pancreas, the resulting fatty acids combining with lime salts. Indeed, Langerhans, who first advanced this view, was able to produce fat-necrosis in the subcutaneous fat

¹ *Boston Med. and Surg. Jour.*, xxxv., 1889.

of a dog by the injection of pancreatic extract; and Hildebrand observed fat-necrosis in the pancreas, omentum, and mesentery after deligating all the vessels of the splenic end of the pancreas, which he tied off so as to hinder absorption of the secretion by the blood-paths. Fat-necrosis was also obtained by placing pieces of the pancreas of one animal into the peritoneal cavity of another. Similar results were obtained by Williams. Flexner¹ finally isolated the fat-splitting ferment from areas of fat-necrosis, and produced fat-necrosis by introducing steapsin into adipose tissue.

Necrosis with Gangrene.—Gangrene is a term applied to certain peculiar changes taking place in dead parts. It appears in two forms, as dry gangrene, or mummification, and as moist gangrene.

Dry gangrene occurs in superficial parts of the body which are freely exposed to the air, so that the fluids in the dead tissues evaporate rapidly, the dryness rendering infection with saprophytic bacteria difficult or impossible. The classic example of dry gangrene is the senile gangrene of the extremities, which usually depends upon necrosis due to anemia; here the tissues become dry and hard, brownish or black, according as much or little hemoglobin is diffused through the necrotic parts during the mummification (Fig. 16).

Moist gangrene develops when a necrotic part of the body becomes the seat of decomposition. A necrotic tissue which is infiltrated with blood and other fluids offers favorable conditions for infection with saprophytic and other bacteria, in consequence of which decomposition and putrefaction of the tissues take place. These lead to greenish and black discoloration of the parts and to the production of foul odors, various gases, and poisonous substances (among which are ptomaines), until finally softening and total disintegration occur. During moist gangrene the resorption of poisonous products may cause a so-called putrid intoxication (sapremia). Moist gangrene



FIG. 16.—Senile dry gangrene of the lower extremity.

occurs usually in tissues that are naturally exposed to infection with saprophytic micro-organisms, as the lungs, the intestinal canal, the external genitals, the uterus, and the extremities, as well as the cutaneous surface in general. The appearances and consequences of moist gangrene of these

¹ *Jour. Exper. Med.*, ii., 1897.

various organs and tissues are described more fully in the sections on Special Pathologic Anatomy.

The causes that lead to necrosis with consecutive dry or moist gangrene are very numerous.

Diseases of the Blood-vessels.—The most important vascular disease in its relation to necrosis and gangrene is arteriosclerosis. The rigid wall and the narrowings, dilatations, and tortuosities of sclerotic arteries interpose decided obstruction to the blood-current, and favor thrombosis and embolism. It is especially in the extremities that gangrene arises in consequence of arteriosclerosis. The thrombosis may be the primary event, or it may occur secondarily in an already gangrenous part, and causes insurmountable hindrances to the re-establishment of the circulation. Embolism from thrombic deposits upon sclerotic heart-valves or upon rough places in the aorta may be followed by gangrene, because of the insufficiency of the collateral circulation through the diseased vessels and the increased liability to secondary thrombosis on account of the roughness of the wall. Cardiac insufficiency and the resulting passive congestion and edema present conditions that are favorable for the development of moist gangrene.

Nerve-lesions.—Necrosis and gangrene are liable to arise in consequence of central or peripheral nervous diseases involving the trophic innervation, particularly when these are aided by pressure, circulatory disorders, mechanic or thermal injuries.

Symmetric gangrene of the hands, feet, or other parts of the body (Raynaud's disease) has frequently been ascribed to trophic lesions, but undoubtedly some instances depend upon a symmetric arteriosclerosis. There are also peculiar forms of gangrene of the skin, affecting not rarely the external genitals, the causes of which are obscure.

Anesthetic leprosy is usually accompanied by extensive necrosis and ulceration that leads to great mutilation. Here the anesthesia exposes the parts to all forms of external injury, mechanic as well as thermal, and to infection, which undoubtedly plays an important role in causing the necrosis of the enfeebled tissue.

The acute decubitus, or bed-sore, that develops in diseases of the spinal cord is generally attributed to trophic disturbances. On account of paralysis the patient sometimes occupies the same position for a long time, in consequence of which the parts chiefly subjected to pressure are rendered anemic, and this anemia favors the development of necrosis. But the acute decubitus of such diseases as transverse myelitis sometimes develops so rapidly that it can scarcely be the result of pressure, and the disturbance of the trophic and vasomotor innervation seems to be the essential cause.

Extremes of Temperature and Chemical Agents.—Extreme heat and extreme cold directly destroy the vitality of tissues. After exposure to extreme cold—congelation—dry or moist gangrene may follow, depending entirely upon external conditions. Tissues may be destroyed by contact with strong chemical agents, as sulphuric and other acids. Direct mechanic violence, such as crushing injury, also produces necrosis. Thermic, chemical, and mechanic agents may lead to necrosis more indirectly by first so changing the vessels of a part that the circulation is permanently arrested.

Local Pressure.—The formation of a bed-sore in a patient with some severe disease, like typhoid fever, is the result of pressure upon a prominent part, such as the promontory of the sacrum, the pressure causing

anemia and death of the tissue. In many of these cases the weak state of the heart favors the occurrence of necrosis. Secondary infection may ensue and greatly hasten the destruction. The pressure of hard foreign bodies may cause perforation (due to necrosis) of the internal organs, as perforation and gangrene of the vermiform appendix by fecal calculi and perforation of the gall-bladder by biliary calculi.

Ergot-intoxication.—Chronic poisoning with ergot leads to persistent contraction of the arterioles and necrosis from anemia. Kobert¹ produced necrosis in the cock's comb and tongue by feeding with ergot.

In man the necrosis occurs first in the ends of the extremities, and most readily in the case of persons with sclerotic arteries.

Progressive Emphysematous Gangrene.—This is a form of infection with *B. aërogenes capsulatus*, the bacillus of malignant edema, or some other anaërobic bacillus, that results in great serous exudation and immediate death of the tissue, followed by the production of gas. The process spreads very rapidly, and may convert an entire extremity into a swollen, crepitating, greenish mass, infiltrated with serous and bloody fluid. The patient usually dies early from general intoxication.

The necrotic change sometimes produced by the *x*-ray has been called white gangrene ("x-ray burn"). The genesis of white gangrene is not understood. It has been assumed that it results from destruction by the *x*-ray of the nerves of the affected part;² but this theory has not yet been confirmed by histologic examinations in early stages of the necrosis.

From the foregoing it will be seen that necrosis and gangrene may develop under a variety of conditions that frequently operate together. The essential causes are in their nature (*a*) mechanic, chemical, or bacterial; (*b*) thermal; (*c*) anemic; or (*d*) neuropathic. Regarding the neuropathic causes of necrosis, it must be said that in the majority of instances in which they appear to play a part they are usually associated with circulatory disturbances, mechanic pressure and injury, and bacterial infection, so that it often becomes impossible to say whether the trophic lesions are the essential factor or not.

When gangrene is arrested from any cause, then the necrotic part is loosened from the healthy tissue by a zone of inflammation; after the absorption or removal of the dead tissue regeneration may occur, but the defect usually becomes more or less completely filled with connective tissue.

Necrosis with Softening.—Necrosis with softening, liquefaction, or colliquative necrosis, may occur either primarily or as a change secondary to other forms of necrosis.

Colliquative necrosis occurs primarily in tissues that contain only a little of the fibrin-forming substances, but which are freely bathed in lymph. These conditions obtain particularly in the brain and spinal cord, in which anemic necrosis is regularly associated with softening. The dead tissue changes into a soft mass containing fragments of myelin and broken-down tissue, which gradually become dissolved in the lymph. Admixture with blood and hematogenous pigment may give the softened area a red, brown, or yellow color. A connective-tissue sac may form around the fluid, a cyst resulting; or complete absorption and cicatrization may take place. In the process of resorption of softened and degenerated material large wandering

¹ *Ueber die Bestandtheile und Wirkungen des Mutterkorns*, 1884.

² Hopkins, *Phila. Med. Jour.*, 1899.

cells filled with detritus and fatty drops and granules, and known as granule-cells, appear. They may accumulate in the sheaths of the vessels.

In the heart-muscle necrosis due to anemia sometimes results in softening. Purulent processes are also accompanied by liquefaction of tissue.

Softening occurs as a secondary process in areas of coagulation necrosis or of mucoid degeneration, in thrombi, and in fibrinous inflammatory exudates, partly as the result of peptonization, partly on account of infiltration with serous fluid. In diseased blood-vessels, together with the formation of new connective tissue in the intima (arteriosclerosis), hyaline degeneration and granular disintegration with liquefaction often take place; cholesterolin crystals may appear, as is the case also in other foci of disintegration. The softened mass is often designated atheromatous material. In the stomach and duodenum necrotic tissue is digested by the gastric juice, giving rise to peptic ulcers.

Coagulation Necrosis. Caseation.—Coagulation necrosis is characterized by the formation in the necrotic tissue of fibrin or of substances morphologically similar to fibrin. Theoretically, coagulation of fibrin would result whenever the necrosis furnished the nucleoproteid termed fibrin-ferment, because the surrounding lymph contains fibrinogen, although only in small quantity. That fibrin is actually formed in necrotic foci can be positively demonstrated in many instances by the use of Weigert's specific fibrin stain. Whether all the necroses commonly included under the term coagulation necrosis, in accordance with the teachings of Cohnheim and Weigert, are in reality instances of fibrin formation may perhaps be questioned. Many of the necroses usually described as examples of coagulation necrosis are defined by some as hyaline degeneration (von Recklinghausen), and by others as caseation (Thoma). The truth seems to be that nearly all the conditions referred to are characterized by the formation from the protoplasm of the dead cells, and also perhaps from the tissue-lymph, of solid albuminous bodies that greatly resemble fibrin morphologically, and in many instances at least are forms of fibrin, as shown by their positive reaction with the fibrin stain.

In so far as thrombosis depends upon the liberation of the fibrin-ferment by dying cells, it is in a way correct to refer to the thrombus as an example of coagulation necrosis. Inflammatory exudates of various kinds also undergo coagulation with the formation of fibrinous masses; and in the so-called diphtheric inflammations of mucous membranes there is a more or less extensive necrosis of the mucosa, with the formation of fibrinous clumps and granules, and thick and thin threads, that are in part the result of coagulation of the dead cells, in part due to coagulation of the vascular exudate and of blood-corpuscles.

Many of the focal necroses of toxic and bacterial origin already considered are undoubted instances of coagulation necrosis. Chemical agents, such as the mineral acids, carbolic acid, corrosive sublimate, cause a coagulation necrosis of the tissues with which they come in contact.

Necrosis of striated muscle is followed by transformation of the contractile muscle-plasma into glistening homogeneous masses without transverse striæ. This change was designated by Zenker as waxy degeneration of muscle. Friedreich, Weigert, and others look upon it as due to a coagulation of the muscle-plasma. It is observed especially in febrile diseases, such as typhoid fever; and it is assumed by some that on account of loss in

consistence and firmness, due to the fever and toxic influences, the fibers separate readily upon muscular contraction. The change is found oftenest in the muscles of the abdominal wall and in the adductors of the femur. The same condition is observed in the ends of healthy muscles that have either been torn or cut across. The tears occur preferably parallel to the transverse striæ; the resulting fragments contract slightly, are homogeneous and refractile, and are without transverse striation.

Muscles that have undergone this change in the course of febrile disease present to the naked eye a lusterless, opaque, pale, grayish-red appearance. The regenerative processes that ensue after necrosis in muscles are considered elsewhere.

Occlusion of terminal arteries in the kidneys and the spleen, from embolism or other cause, results in necrosis due to anemia of the parts nourished by the occluded branches, and the so-called *anemic infarct* is formed, which may be changed into a red or hemorrhagic infarct in consequence of a secondary infiltration with blood. In either case coagulation occurs in the protoplasm of the cells and of the intercellular lymph, and, in the case of the red infarct, of the blood-plasma. The cells are changed into homogeneous hyaline masses, lying in a granular or reticulated substance; subsequently the dead tissues disintegrate into a granular amorphous detritus, while the red blood-corpuscles fall into fragments and give rise to pigment particles. During the subsequent changes a hemorrhagic infarct may lose its color.

According to Schmaus and Albrecht, anemic necrosis of the kidney from experimental ligation of the renal artery may be followed by a breaking up of the nucleus of some of the cells into fragments (*karyorhexis*), preceded by a transposition of the chromatin filaments; this they regard as a necrobiotic change in the nucleus. Ordinary karyolysis is observed at the same time. Albrecht believes that in the normal state protoplasm is fluid, and that when coagulation occurs the protoplasm becomes the seat of a precipitation in drop-like form (the so-called *tropfige Entmischung*).

In the course of time infarcts either become absorbed and replaced by a scar, or are encapsulated and infiltrated with lime salts.

Caseation is the term applied to postnecrotic changes that give the dead tissue a similarity to various forms of cheese. The substance is more or less firm, dry or sometimes viscid, and yellowish or grayish-white. Microscopically the mass is granular or contains somewhat homogeneous flakes. The original structure of the tissue is partly or wholly lost, the nuclei are absent or refuse to stain, or are broken up into dust-like particles of chromatin. At times a granular network may be observed, on which account caseation has also been considered a form of coagulation necrosis; but the fibrin is small in amount, and often is entirely absent. The chemical composition of caseous material is not known, and it is very probable that various substances are included under the same name. In many instances the caseous material is more soft, and consists then of a fatty and albuminous granular detritus. It is probable that the variable consistency of caseous material depends upon changes in the amount of fluid present in the area, which again may depend upon local conditions. An interchange of substances by diffusion, or in other ways, probably takes place between the surrounding tissue and the cheesy focus.

Caseation occurs especially in tuberculous areas. It constitutes the

characteristic form of necrosis, or necrobiosis, in the miliary and conglomerate tubercles, and in diffuse tuberculous infiltration. The necrosis that results in caseation is due in part to the poisonous action of the tubercle-bacillus and its products, in part to insufficient blood-supply of the new tissue.

Caseation also occurs in syphilitic areas, in certain rapidly growing tumors, and in some non-tuberculous inflammatory infiltrations in the lungs. The coagulation necrosis of infarcts is sometimes regarded as caseation.

Caseous masses may be completely absorbed; or they may be surrounded by a wall of connective tissue, may undergo softening, inspissation, or calcification.

SIMPLE ATROPHY.

Atrophy is the shrinking of an organ or tissue, due to decrease in the size and number of the cells, without any evident change in structure or in chemical composition. It is a retrogressive process of parts well formed and, in proportion to the age of the organism, well grown.

Atrophy occurs physiologically, as, for instance, in old age, when a varying degree of shrinking takes place in the tissues of the body. Here the shrinking appears to be due to a diminished regeneration of cells that have been worn out, so that what may be called the normal senile atrophy is due not so much to increased waste as to diminished repair.

The thymus undergoes almost complete involution early in life, and the female generative organs become atrophic after the menopause.

The mammalian fetus presents many structures which shrivel and disappear, leaving perhaps but remnants as their functions either become unnecessary or are assumed by other organs. As examples may be mentioned the vitelline duct, many of the vessels concerned in the fetal circulation, the thyroglossal duct, the Wolffian bodies, and various canals connected with the organs of generation.

Simple atrophy, or atrophy in the strict sense of the word, is due to a decrease in the size or number of cells of an organ, or to both these changes, without the intervention of any special changes in the structure or chemical composition of the cells. Degenerative atrophy, on the other hand, is preceded by degenerative changes in the protoplasm and nuclei of the cells, and is a consequence of some of the familiar forms of degeneration about to be described.

The cells microscopically present no demonstrable changes in the earlier stages of simple atrophy, except diminution in size and perhaps a slight change in form, and in some instances an increased pigmentation, as in the heart-muscle and in the liver. In advanced stages the cells may be greatly shrunken and deformed, becoming converted into firm, irregular masses without visible nuclei, disintegration and absorption finally taking place. The increase in pigmentation observed in some tissues may be a real increase in pigment or an apparent or relative one, the pigment becoming more clearly visible as the cells shrink. In the so-called *brown atrophy* of the heart the heart-muscle presents a brownish color, which is readily recognized with the naked eye, and which depends upon an accumulation of a brownish granular



FIG. 17.—Brown atrophy of heart-muscle cells in chronic pulmonary tuberculosis. $\times 260$.

pigment in the vicinity of the poles of the nuclei of the muscle-cells (Fig. 17). Atrophic ganglion-cells are usually highly pigmented; vacuolation and a homogeneous transformation of the cytoplasm also occur, demonstrable by staining with Nissl's method (Fig. 18). When striated muscle undergoes atrophy the fibers become narrow and the striations indistinct; simultaneously there may be increase in the fat, which replaces the disappearing muscle.

Diminution in the size as well as in the weight of atrophic organs depends, as stated, upon the decrease in the size and number of their cells. It is to be noted, however, that in glandular and other organs, as well as in muscles and bones, it is the specific tissue-elements that atrophy, and not the connective-tissue framework. The tubular epithelium of the kidney, the hepatic cells, and the ganglion-cells of the brain and spinal cord may undergo complete atrophy without appreciable decrease in the connective or glia-tissue. In this manner an atrophic organ may become harder and firmer than normal (induration). If the atrophy of an organ occurs in equal degree in

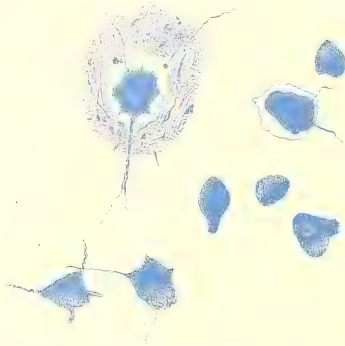


FIG. 18.—Atrophy of the ganglion-cells in the anterior horns of the spinal cord in amyotrophic lateral sclerosis. Fixed in absolute alcohol; stained with methylene-blue (Nissl's method). $\times 300$.

all parts, the surface presents the normal contour; but if it occurs irregularly, the surface becomes uneven and granular.

In the case of the lungs and the bones atrophy may take place without any special changes in external form or volume, the process involving the walls of the pulmonary alveoli, and in the bones the medullary spaces and Haversian canals, the lumen of which becomes enlarged (eccentric atrophy, osteoporosis). The decrease in weight will in such cases give a correct notion of the extent of the atrophy.

Atrophy of the connective tissues, especially of adipose tissue, is of common occurrence.

The **causes** of simple atrophy are manifold, and it is customary to consider the etiologic varieties under the following headings:

The Atrophy of Inactivity or Disuse.—An intimate relation exists between nutrition, function, and growth of tissue. Total or partial functional inactivity leads to diminution in the nutritive supply. The vascular mechanism is so arranged that where the greatest functional activity exists

there the blood-supply is best; *vice versa*, functionless tissues receive less nourishment. Both inability to perform the functions as well as the removal of the necessity for the functions may lead to atrophy. Inactive parts therefore atrophy.

Loss of the necessity of function appears to be the essential cause of the atrophy or involution of the fetal structures already enumerated, and also of various highly specialized organs in certain animal species. Thus, the eyes of the denizens of the Mammoth Cave of Kentucky are of no service because light never penetrates its vast recesses; the necessity for the function of vision no longer exists, and hence the eyes of these animals have gradually suffered atrophy, so that at the present time the descendants of animals once possessing perfect eyes have only blind remnants. In several forms of deep-sea fishes, especially those which have descended to such great depths that few if any rays of light reach them, the eyes are rudimentary, and in some cases are covered with skin (Bland Sutton).¹

Atrophy from inability to carry on function is well illustrated in the great wasting which occurs in all the structures of an extremity rendered functionally inactive or useless by a tumor, a serious deformity, or on account of paralysis.

Pressure-atrophy.—Atrophy takes place when a tissue is exposed to prolonged increase in the normal pressure. This form of atrophy is frequently observed in the course of various pathologic processes. It undoubtedly depends in part upon circulatory disturbances, in part upon direct injury to the cells. Pressure-atrophy is illustrated by the shrinking of the liver-cells adjacent to a distended central vein the seat of passive congestion; by the gradual disappearance of parenchymatous cells when compressed by contracting cicatricial tissue, as in chronic interstitial myocarditis and cirrhosis of the liver; by the so-called "corset liver," the characteristic deformity of which is due to atrophy of the liver along the line of pressure by the costal arch; by the hollowing out and disintegration of the vertebræ (Fig. 19) and parts of the bony thorax under the continuous pressure of aneurysms of the aorta; and by the thinning of the skull in various forms of increased intracranial pressure.

Senile and Marantic Atrophy.—Atrophy occurs to a marked degree in the condition described as premature senility, and in certain diseases and conditions accompanied by great wasting and exhaustion (marasmus). The atrophy of premature senility may be considered theoretically as due to the scanty power of regeneration and repair of congenitally imperfect and enfeebled cells. Practically, however, the diminution of arterial blood-supply due to disease of the arteries, and disturbances



FIG. 19.—Disintegration of the bodies of the vertebræ due to the pressure of a thoracic aneurysm.

¹ General Pathology.

of nutrition on account of diseases of the digestive tract or of the nervous system, often appear to play an essential role.

The general atrophy that occurs in starvation must be ascribed to absence of nourishment; the atrophy of chronic wasting diseases, such as tuberculosis, carcinoma, leukemia, and also of certain acute infections, may be attributed in part to deficient nourishment, and in part to general poisoning with toxic substances produced by the morbid processes which directly lower the vitality of the cells. The atrophy in these conditions is frequently accompanied by degenerations of various kinds. Imperfect regeneration also plays a part in the resulting atrophy. Local interference with the blood-supply, as occurs in consequence of diseases of the arterial walls, causes local atrophy when the anemia develops gradually; sudden, absolute anemia is followed by necrosis.

Neurotic Atrophy.—The state of the central nervous system is of great importance as regards the nutrition of the body. The classic examples of neurotic or neuropathic atrophy are seen in the rapid wasting of the muscles (Fig. 20) and of the nerves after destruction or disease of the anterior horns

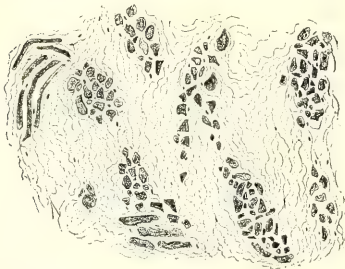


FIG. 20.—Atrophy of skeletal muscle following degeneration of the ganglion-cells of the anterior horns of the spinal cord. $\times 175$.

of gray matter in the spinal cord and of the bulbar nuclei. The ganglion-cells in the anterior horns are the trophic centers of the motor neurones of the second order, and exert also marked trophic influences upon the corresponding muscles. Undoubtedly many factors operate in producing the muscular atrophy of central origin: the paralysis that follows removal of the nerve-supply induces inactivity; vaso-motor disturbances are certainly present, which may cause further nutritive disorders; and then the

probable direct trophic influence of the ganglion-cells is also removed.

In disease of the nerves of the face *facial hemiatrophy* sometimes develops; and fetal or infantile diseases of a cerebral hemisphere may be followed by atrophy of the opposite half of the body. In rare cases the hemiplegia of adults, though dependent upon a cerebral lesion, is followed by an atrophy that is only in part explicable by disuse; in part it seems to be trophic.

The term atrophy is applicable to the retrogressive processes above outlined, as it occurs in tissues or organs well formed and developed, in contradistinction to hypoplasia and aplasia, which are terms used to designate imperfect developmental conditions. *Hypoplasia* is the incomplete development of a part of the body. Growth may be arrested during fetal life or during the postnatal period of development. Hypoplasia may depend upon causes originally present in the germ-cells, or upon external influences that arrest or limit the further growth of the "anlage." When the arrest occurs late in fetal, or in postnatal, life the nature of the condition seems to correspond to certain forms of atrophy. Thus, diseases of the thyroid gland, or disuse in consequence of deformity or inflammation, may limit or disturb the normal growth of growing bones, and absence of the ovaries may arrest the

growth of the uterus. On the other hand, many such conditions as are observed in some dwarfs, in the rudimentary development of extremities, and in the almost complete absence or limited development of many organs, such as the brain, the intestines, the kidneys, the lungs, the uterus, and the liver, must be referred to causes inherent in the germ-cells, or to diseases and accidents in the earliest periods of fetal life.

If an organ or part of the body fails entirely to develop, the condition is one of *aplasia*, or *agenesia*; it may depend either upon a congenital absence of the "anlage" in question or upon a direct destruction or complete atrophy of the part after its development had begun. The further consideration of hypoplasia and aplasia belongs to teratology.

DEGENERATIONS AND INFILTRATIONS.

Amyloid Degeneration.—Amyloid, waxy, or lardaceous degeneration is a peculiar retrogressive process due to the formation or deposition in various organs of a serum-albumin of slight solubility and of a homogeneous appearance, which gives a mahogany-brown color reaction with iodine, and a rose-red with methyl-violet or gentian-violet.

Amyloid degeneration develops, as a rule, in several organs at the same time, but without any regular order; most frequently it occurs in the spleen, the liver, the kidneys, the stomach, the intestines, the pancreas, the adrenals, the thyroid gland, and the lymphatic glands; but it may also occur in the heart, the aorta, the muscles, adipose tissue, the uterus, and the ovaries.

Organs the seat of advanced amyloid degeneration are usually much enlarged. In the case of the liver the margins are thick and rounded, the consistency greatly increased, so that the organ is firm and rather inelastic; the cut surface presents large, irregular areas of a dry, somewhat glistening, homogeneous appearance, and thin sections of it are translucent and not unlike the fat of bacon. The translucent areas stain brown with watery solutions of iodine. When the process is less pronounced, in its early stages, or when it is accompanied by fatty or other changes, or when it occurs in localities such as the heart, the aorta, or in adipose tissue, it may be necessary to resort to microchemical examination in order to demonstrate the presence of amyloid material.

The characteristic iodine reaction of amyloid material is obtained in the following manner: First the blood is washed from the surface with water; then the reaction of the tissue is rendered acid by pouring over it a little acetic acid, although this is not absolutely necessary; this is followed by a short bath in a solution of iodine in iodide of potassium (iodine, 1 part; potassium iodide, 10 parts; distilled water, 100 parts), which is washed away with water. The amyloid material will be found stained a deep reddish-brown or mahogany-brown, while the surrounding tissue is of a straw-yellow color. Microscopic sections of fresh tissue, made with the double knife or freezing microtome, may be stained in precisely the same manner. It is well, however, to use a more dilute iodine solution. Under the microscope the amyloid material is of a brighter reddish-brown color. The iodine reaction is also obtainable with hardened tissues.

The acetic acid is added in order to insure an acid reaction of the tissue; when the tissue has become alkaline in reaction from decomposition, then the

brown color of the amyloid material may fail to develop, on account of the formation of the alkaline iodids. If the tissue, after having been stained brown with iodine, is treated with dilute sulphuric acid (5 per cent.) or a solution of chlorid of zinc, the amyloid areas become very dark brown, grayish-brown, violet, greenish-blue, or blue. This reaction is inconstant, and the colors are generally a little mixed.

Oddi and also Krawkow have recently shown that amyloid substance is a compound of chondroidin-sulphuric acid and albumin. Krawkow found this compound a normal constituent of cartilage and all structures rich in elastic tissue, particularly in the blood-vessels. In its pure state amyloid is entirely free from phosphorus and does not give the iodine, but gives the methyl-violet, reaction. The iodine reaction as ordinarily obtained seems to depend upon physical conditions, the amyloid substance assuming the brown color with iodine when in a compact state.

For the purpose of a closer microscopic study of tissue the seat of amyloid degeneration, the staining with methyl-violet or gentian-violet solution gives the best results. The microscopic sections of fresh tissues or of tissues hard-

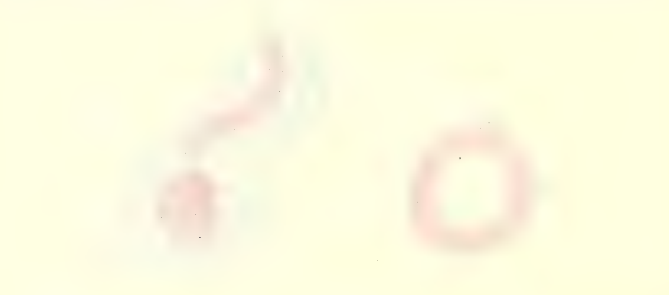


FIG. 21.—Amyloid degeneration of the kidney in chronic pulmonary tuberculosis: *a*, degeneration of the capillary network of a glomerulus and of the wall of the afferent vessel; *b*, degeneration of the media of a small artery. Alcohol hardened, stained with methyl-violet, decolorized with acetic acid; amyloid material pinkish red, normal tissue bluish. $\times 75$.

ened in alcohol or formalin are brought for a few minutes into a watery solution of methyl-violet; they are then washed in acetic-acid water, mounted, and examined in glycerin. The amyloid material will be stained a bright or ruby-red, while the surrounding tissues are blue or bluish-violet (Fig. 21). By careful decolorization in the acetic-acid water the nuclei of the tissue will appear deep violet, while the amyloid substance is bright red, so that the relation of the amyloid material to the cells of the tissue in which it is found can be made out very clearly.

By studying such preparations it is found that amyloid material is formed or deposited primarily in the ground-substance of the blood-vessels and the connective tissue, especially in the middle coat of the smaller arteries.

In the kidneys the process commences in the intertubular arteries and in the capillary tufts of the glomeruli. Homogeneous masses of varying size and shape seem to crowd the muscular fibers of the media apart, while the endothelial lining remains intact. The muscle-cells may show irregularities in form, due to shrinking or atrophy from pressure, and in many cases the

entire media may appear to have been replaced by amyloid material. The capillary loops of the glomeruli are greatly swollen and homogeneous, and the amyloid material may appear between the tubules of the kidney outside the vessels as well as in the tunica propria of the tubules.

In the liver the amyloid material appears first between the capillary endothelium and the rows of liver-cells; here it forms thick, homogeneous layers, between which are partly normal, partly atrophic, or fatty hepatic cells. Amyloid material does not appear to develop in the interior of the liver-cells. In the gastro-intestinal mucous membrane the amyloid material appears first in the walls of the vessels; in the spleen the walls of the smaller arteries and veins are usually involved, but the degeneration quite often confines itself to the Malpighian bodies, which may become greatly enlarged and not unlike grains of boiled sago (*sago-spleen*); the trabeculae and fibers of the reticulum also become thickened. In fat tissue the amyloid material may appear in the walls of the vessels as well as in the fibrous tissue and in the membrane of the fat-cells; and in striated muscle it develops in the internal perimysium and the sarcolemma. The occurrence of amyloid degeneration of the muscle-cells proper has not been proved to general satisfaction.

On account of giving a brown color reaction with iodine and a blue color with sulphuric acid and iodine, Virchow¹ saw a certain resemblance between amyloid material and starch; and hence the name amyloid, which he originated. While starch (*amylum*) is a carbohydrate, Kekule and Friedreich, and others, soon demonstrated that amyloid material is an albuminous body, characterized by insolubility in water and by great resistance not only to acids and alkalis, but also to the action of gastric juice and to decomposition.

The causes of amyloid degeneration are not clearly understood. Observation has established the fact that in the majority if not in all of the instances it occurs as a secondary process in certain general, chiefly infectious, diseases accompanied by grave disturbances of nutrition. It is especially in connection with chronic tuberculosis (lungs, bones, and joints), chronic suppuration (osteomyelitis, actinomycosis), severe forms of syphilis, and chronic dysentery, that extensive amyloid degeneration takes place. Carcinoma, leukemia, and severe malarial infection occasionally lead to amyloid degeneration; and Ziegler states that at times it develops without any preceding disease. Bland Sutton remarks that in horses amyloid degeneration may occur independently of previous disease. Czerny claims to have produced it in dogs by long-continued experimental suppuration due to injection of turpentine, but Krakow and Lubarsch were not able to confirm this statement. Krakow² describes a series of experiments in which he claims to have succeeded in producing amyloid degeneration in rabbits and in chickens by the repeated injection, in increasing quantities, of bouillon cultures of *Staphylococcus pyogenes aureus*. He also produced amyloid change by using the toxin of *Bacillus pyocyaneus*. The degeneration appeared in from one and one-half to two months after beginning the injections. Cohnheim observed that in man the degeneration could develop in from two to three months. Maximow and Davidsohn have also produced amyloid material by experiments similar to those of Krakow.

While it is evident that amyloid degeneration stands in close relation to

¹ *Virchow's Archiv*, v., vi., viii., xi.

² *Arch. de méd. exp. et d'anat. pathol.*, x., 1898.

the general nutritive disorder and the chronic intoxication (cachexia) present in the diseases mentioned, and also in the animals experimented upon, yet the exact histogenesis of the amyloid material remains unexplained. Several hypotheses have been advanced. Thus, it has been thought that the parenchyma-cells are directly changed into amyloid substance; but this theory does not accord with the microscopic appearances, which clearly show that the material first appears in the ground-substance of the connective tissue and the vessels. Von Recklinghausen¹ advances the hypothesis that the cells of the organs affected eliminate a homogeneous material which stiffens in the tissue-spaces into the characteristic masses of amyloid material. The insolubility of amyloid material would seem to exclude the idea that it could circulate dissolved in blood and be deposited in the tissues. The constancy with which the material appears in the walls of the vessels points, however, to some relation between its formation and the blood; and at the present time the general opinion seems to be that in the diseases in connection with which the degeneration appears there is present in the blood a substance which is either precipitated or deposited in the tissues as amyloid material or unites with the tissue-juices to form this peculiar substance. If it is possible, as seems to have been shown, that amyloid degeneration may be produced experimentally, the question concerning the histogenesis of the material will undoubtedly receive further elucidation. Czerny has advanced the opinion that in the early stages amyloid material is formed in the local foci of suppuration, and is carried to the internal organs by the leukocytes. He bases this opinion upon finding cells giving the amyloid reaction in the pus and in the blood of animals showing later amyloid degeneration of the spleen.

Amyloid degeneration is always fraught with serious consequences. As far as is known at the present time, amyloid material once formed is probably not reabsorbed. Krakow showed that in the rabbit experimentally produced amyloid degeneration of the spleen might disappear by absorption of the material, but it is not known that this can occur in man. A probable exception to this statement is the fact observed by Raehlmann and others, that so-called amyloid tumors of the conjunctiva may undergo complete absorption after partial removal. When amyloid material is introduced into the peritoneal cavity of rabbits it is gradually removed by giant cells, which shows that the material is susceptible of absorption. Giant cells enclosing amyloid material have also been found in local amyloid deposits (see below). While the diseases that lead to amyloid degeneration are of the most serious nature, it is evident that the permanent tissue-changes induced by this process must tend to aggravate the grave general condition that already exists. Thus, the changes in the vessel-walls lead to narrowing, and even occlusion, of the lumen, with permanent disturbance of the circulation; and the pressure of amyloid masses upon the adjacent cells causes atrophy. Fatty degeneration and atrophy of the special tissue-cells are consequently always observed in organs undergoing the amyloid change, partly as the direct result of the local action of the amyloid material, partly as the result of the general cause that gave rise to the amyloid degeneration.

Local Amyloid Formation and Corpora Amylacea.—In addition to the general amyloid degeneration, which usually involves several organs at the

¹ *Allg. Path. des Kreislaufes und der Ernährung*, 1883.

same time, and which develops under special conditions, there occurs also, undoubtedly from local causes, a purely local amyloid formation, either in the form of amyloid infiltration of tissue, to which belong the so-called amyloid tumors, or as free amyloid concretions.

Local infiltration of amyloid material has been observed in cellular granulation-tissue, as in the conjunctiva and in ulcers of the leg, in scars and chronic connective-tissue proliferations, as, for instance, in syphilitic cicatrices of the liver and of the larynx, as well as in syphilitic lymphadenitis, and also in various tumors—*e. g.*, of the larynx and of the stomach. Usually the amyloid substance occurs in small masses, but occasionally also in larger foci; the material appears in the ground-substance of the tissue and in the vessel-walls; although some authors state that the cells themselves may become hyaline and give the amyloid reaction (Raehlmann). The amyloid material has frequently been observed in these situations in connection with hyaline degeneration.

Tumor-like amyloid masses without any definite connection with inflammatory processes are also occasionally met with, especially in the conjunctiva, the root of the tongue, the larynx, and the trachea. These masses may reach considerable size and become very hard; they are commonly called amyloid tumors.

Free amyloid concretions, or corpora amylacea, are found almost constantly in the tissues of the central nervous system. They occur especially in the ependyma of the ventricles, but also elsewhere in the brain and spinal cord, more particularly in areas in which the nerve-fibers have undergone degeneration.

Corpora amylacea occur also quite regularly in the follicles of the prostate (Fig. 22) after puberty; furthermore, in the lungs, in fibrinous exudates, hemorrhagic extravasations, and chronic fibroid processes, or free in the alveoli in emphysematous parts. They have also been found in carcinomas.

These bodies, which usually give the amyloid reaction with iodine, present in the main a concentric arrangement; in the center may be irregular fragments or masses, or hematoidin crystals in case they have formed in hemorrhagic foci, as in a pulmonary infarct; those found in the central nervous system are usually small compared with those from the prostate. It is generally believed that they are formed by the coalescence of the remnants of desquamated and degenerated cells.¹ In the nervous system some believe they arise from the nuclei of the glia-cells, while others claim they are developed from the fragments of degenerated axis-cylinders. In many

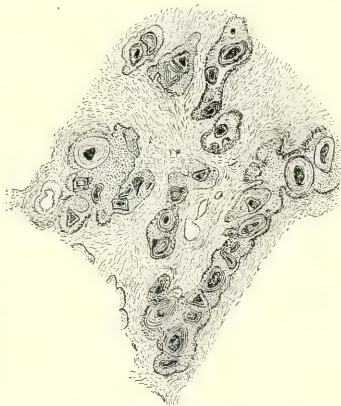


FIG. 22.—Amyloid concretions (*corpora amylacea*) in the gland-tubules of the prostate of a man thirty-two years old. $\times 150$.

¹ Seigert, *Virchow's Archiv*, cxxix, 1892.

respects some of the amyloid bodies resemble the globular hyaline formations to be described.

Hyaline Degeneration.—Hyaline degeneration takes place especially in connective tissue, and renders it homogeneous and structureless. The hyaline substance into which the connective tissue is converted or by which it is replaced has not yet been shown to have a distinct chemical entity; it resembles amyloid material, but is distinguished from it by the absence of the iodine reaction. Hyaline material has no constant staining reaction, although with Van Gieson's stain it assumes a bright-red tinge. Like amyloid degeneration, hyaline also attacks by preference the walls of the blood-vessels; but hyaline degeneration does not show any such marked etiologic relation to chronic suppuration and infection as amyloid, and its distribution in the body is more erratic.

In the walls of the smaller blood-vessels the hyaline material appears first outside the endothelial lining, in the form of homogeneous masses. Gradually the wall becomes thicker and the lumen smaller; and finally the latter

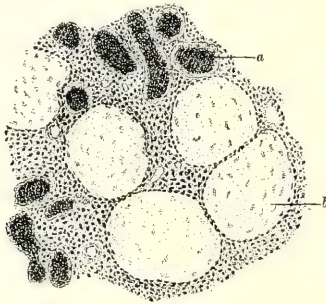


FIG. 23.—Hyaline degeneration of the glomeruli and colloid material in the tubules in the vicinity of an anemic infarct in the kidney; *a*, colloid material; *b*, hyaline glomeruli with much round-cell infiltration about them. $\times 150$.

may disappear entirely. Hyaline degeneration of the smaller vessels is observed in the capillary tufts of the glomeruli of the kidney (Fig. 23), in the brain, in the lymph-glands, and also in the meninges in tuberculous meningitis (Fig. 24). In the last it might be confounded with caseation were it not for the fact that it often occurs in the walls of vessels surrounded by recent tuberculous proliferation in which no degeneration has occurred (Guarnieri).

Hyaline degeneration also occurs in the thickened intima of sclerotic arteries, and in heart-valves the seat of chronic fibrous endocarditis. In these localities the hyaline material frequently becomes softened and infiltrated with calcareous particles. It is also found in the connective tissue of the myocardium, the intestines, in old scars, in the stroma of many tumors, and in the thyroid gland (Fig. 25), especially when goiter is present. The connective tissue becomes homogeneous and structureless, the nuclei disappearing almost entirely, while the specific tissue-elements gradually atrophy.

The exact cause of hyaline degeneration is not understood. It occasionally occurs in conjunction with amyloid degeneration; but any close relation

between the two changes has not been demonstrated. Neither has it been determined whether the process is essentially one of degeneration or infiltration.

The so-called hyaline bodies (Russell's fuchsin bodies) are peculiar globular, homogeneous, extracellular and intracellular formations of vary-

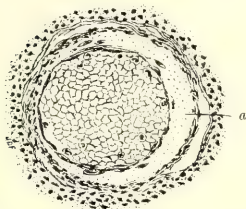


FIG. 24.—Hyaline degeneration of the media of a small artery in the pia in tuberculous meningitis: a, hyaline media, much infiltration with cells in the adventitia. $\times 200$.

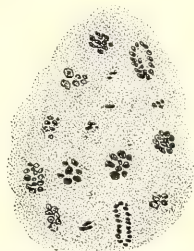


FIG. 25.—Hyaline degeneration of the stroma in the thyroid gland in fibrous goiter. $\times 75$.

ing size; frequently they are aggregated in mulberry-shaped conglomerations. They stain red with the acid-fuchsin, and deep blue with the Gram-Weigert stain (Fig. 26). These bodies occur in many normal tissues and in a great variety of pathologic processes, a favorite place for their study being glandular proliferations of the mucous membrane of the stomach (Hansemann, Thorel); their frequent presence in malignant tumors

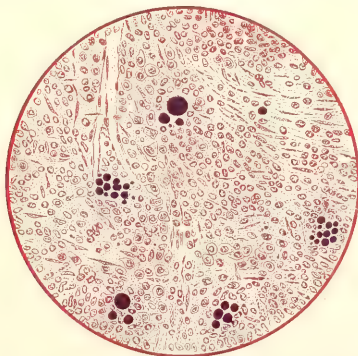


FIG. 26.—Hyaline bodies; chronic appendicitis: carmin and Weigert's stain. $\times 250$.

has led to their being regarded as "cancer parasites" of blastomycetic nature. It is believed that the granules in the oxyphile and basophile cells that are found where organic material is breaking down from any cause may give rise to hyaline bodies, the process partaking of the nature of coagulation. The exact chemical composition of hyaline bodies is not known.

According to its origin, hyaline material as it appears in these bodies may be spoken of as mesoblastic, epithelial (keratohyalin), and blood hyalin (Lubarsch).¹

Degenerative changes in glia-cells may produce glistening masses that stain black with the Weigert-Pal method, red with Van Gieson's method, and bright blue with Weigert's fibrin stain after fixation in Zenker's fluid. First described by Rosenthal, this degeneration has been studied by Barker,² who called it *degeneratio micans*, and showed that the peculiar masses form within glia-cells. So far, *degeneratio micans* has been observed only in gliomas of the spinal cord.

Colloid Degeneration.—Colloid material in its appearance resembles stiffened glue. The substance is usually semisolid, translucent, homogeneous, structureless, and yellowish or brownish in color. The term colloid material does not imply any definite chemical entity. The material differs from mucus in its reactions; unlike the latter, it does not swell in water, is not coagulated by acetic acid, nor is it made turbid by alcohol or chromic acid.

Colloid material occurs physiologically in the follicles of the thyroid gland and the hypophysis; here it is produced by the cells lining the follicles, and, according to a number of investigators, is taken up, as far as the thyroid is concerned, by the lymphatics. Concerning the physiologic importance of this secretion, which contains iodine in the form of thyroiodin, more will be said in the section dealing with the thyroid gland.

An excessive production of colloid material is often observed in the thyroid gland; the follicles then are greatly enlarged and filled with homogeneous masses, so that the gland is much increased in size. The formation of these masses takes place by the coalescence of numerous small drops which arise in the interior of the cells of the follicles, whence they are extruded; at times the entire cell is converted into colloid substance. Similar colloid masses sometimes form by degeneration of the hypophysis. Colloid material, or material of exactly similar microscopic appearance, but in all probability not containing iodine, is often found in the uriniferous tubules and retention cysts of diseased kidneys, and is apparently the result of a degeneration of the epithelial cells. The so-called colloid degeneration in certain forms of carcinoma is probably mucoid in its nature; but in the absence of microchemical reactions and of a definite knowledge of the chemical composition of these jelly-like substances, a correct classification of the obscure changes that lead to their development is not possible.

With Van Gieson's stain colloid material usually strikes an orange-red color.

Mucoid Degeneration.—Mucoid degeneration is the transformation of living tissue into mucus, a transparent, homogeneous, viscid substance. Mucus is a generic term embracing various chemical compounds, known as mucins and pseudomucins. The mucins are nucleo-albumins, and contain nitrogen and sulphur; they swell in water, are precipitated by alcohol and by acetic acid, and are not dissolved in an excess of the acid. They are non-diffusible substances. The pseudomucins are soluble in water and are not precipitated by acetic acid (Hammersten).

Mucus occurs physiologically upon mucous membranes and in mucous

¹ For references, consult *Progressive Medicine*, March, 1899, 241.

² *Am. Jour. Med. Sci.*, cxviii., 1899.

glands, in the contents of joints, tendon-sheaths, and bursas, and in the umbilical cord, where it forms a homogeneous, jelly-like ground-substance. In the mucous membranes the mucus appears especially in the so-called goblet-cells, the protoplasm of which changes into a roundish mass of mucus that appears to fill the cell like a goblet. The mucus formed in the protoplasm of these cells is evacuated and the cells retain their vitality.

The so-called catarrhal inflammations of mucous membranes are characterized by an excessive secretion of mucus by the surface epithelium and the mucous glands. The number of goblet-cells in the membrane appears to be greatly increased (Fig. 27). Furthermore, many of the cells may undergo a total mucoid degeneration of the nucleus as well as of the body, leading to the destruction of the cell. The exudate may contain masses of mucus, in which fragments of such cells are recognizable. The ordinary pus-córpuscles in the exudate may also change into mucus.

Mucoid degeneration also takes place in the epithelial cells of tumors, more especially in carcinomas that originate in the mucous membrane of the gastrointestinal tract, and in the ovarian cystadenomas. Here it occurs chiefly as a mucoid disintegration of the cells, leading to the formation of large homogeneous, structureless masses. In the ovarian cystomas the degeneration results largely in the formation of pseudomucin (Pfannenstiel).

Mucoid degeneration also occurs in the connective tissues; here it is principally the ground-substance that is changed into mucus, although the cells are liable to become involved. Thus, the connective-tissue framework of carcinoma may be transformed into mucoid material. Mucoid degeneration occurs in cartilage and in bone as a senile, retrogressive change, and is also frequently observed to take place in the various mesoblastic tumors, including sarcoma. In such cases the intercellular substance becomes soft and viscid; small clumps of mucus form in the cells, which finally disintegrate and disappear more or less completely.

In the disease known as myxedema, which depends upon disturbance of the functions of the thyroid gland, the subcutaneous tissue is changed into mucoid (myxomatous) material. The exact pathogenesis of this peculiar change is not known.

Mucoid degeneration is, on the whole, a rather mysterious process, the significance of which is not clear nor is its exact etiology understood. It depends upon a chemical process, in which the tissue is changed into mucus. The excessive secretion of mucus in catarrhal inflammations may be looked upon as a favorable feature, in that it protects the membrane, and limits the growth of the invading micro-organisms. Mucus is not bactericidal, but affords a poor soil for the growth of micro-organisms.

According to Levene,¹ the acid radicals in amyloid, mucoid, and colloid materials are similar (chondroidin-sulphuric acid).



FIG. 27.—Mucoid degeneration of the cells of a tubule in the mucous membrane of an inflamed vermiform appendix. $\times 450$.

¹ *Med. Rec.*, 1900.

Cloudy Swelling and Fatty Degeneration.—If one carefully examines the kidney, the heart, or the liver, of persons who have died of typhoid fever, septicemia, or other acute infectious or toxic disease, it will be found that the organ is relatively a little larger than normal, that the consistence is not so firm, but is rather flaccid, and that on the cut surface the tissue presents a grayish-yellow, turbid or opaque, sometimes shining appearance, as though it had been boiled, while the finer markings characteristic of the organ are indistinct; the organ usually contains but little blood.

In a fresh microscopic preparation, made by carefully scraping the cut surface with a knife or by teasing and mounting some of the particles in physiologic salt solution, the cells will appear larger than normal; they are swollen, the protoplasm is clouded and covered with innumerable opaque granules, among which may be refractile glittering points or droplets with darker outlines, so that it is difficult to see the nucleus (Fig. 28), while the finer markings peculiar to certain cells, as those of the kidney, or the

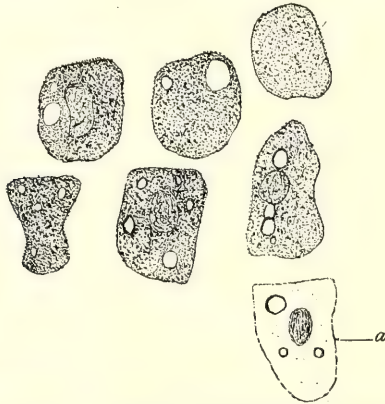


FIG. 28.—Cloudy swelling of the epithelium of the convoluted tubules of the kidney in puerperal septicemia (general streptococcic infection): *a*, cell after application of a weak solution of acetic acid; the granules have become dissolved, but the fat-droplets remain. Fresh teased specimen. $\times 1000$.

striations of the heart-muscle, are no longer clearly discernible. If the physiologic salt solution be replaced by a 1 per cent. solution of acetic acid, which is allowed to run in under the cover-glass, the fine, dust-like granules are dissolved, the protoplasm becomes clear and the nucleus distinct, while the glistening droplets are undissolved, and are recognizable as particles of fat (Fig. 28, *a*). If alcohol or ether be used with another preparation, the granules are unaffected; but the fat dissolves, leaving holes in the protoplasm of the cell. In such preparations cells will be found from which the nucleus has almost entirely disappeared, so that it is not to be seen even after the application of the acetic-acid solution; and some cells will appear to be disintegrating into granular and fatty detritus.

In a given case the relative quantity of fat-droplets and dust-like granules varies in different cells. According as the one or the other of

these changes predominates, the condition is spoken of as cloudy swelling (parenchymatous degeneration) when the granules are most numerous, or as fatty degeneration when the droplets predominate.

Cloudy swelling, parenchymatous, or albuminous degeneration, is, then, a retrogressive process in which the tissue elements disintegrate into albuminoid granules. The free granules described are regarded as albuminoid, because they are soluble in acetic acid, but insoluble in alcohol and ether. The cells affected become clouded, diffusely granular, the normal structure and form are altered, and there is a slight but evident increase in the size of the cells, probably due to the absorption of fluid. The normal granulation disappears. Very often particles of fat are also formed in the protoplasm.

A certain degree of cloudy swelling is compatible with continuance of function and may subside, the cell resuming its normal structure; often, however, the nucleus swells and disappears, while the cell crumbles into a granular or granular and fatty detritus (Fig. 29).



FIG. 29.—Granular and fatty disintegration of the cells of the convoluted tubules in puerperal eclampsia. Fixed in Flemming's solution; stained with safranin. $\times 300$.

Cloudy swelling develops especially in parenchymatous cells, as those of the liver, the kidney, the heart, and other organs; but it may also affect the cells of the stroma of organs, as well as migratory cells.

Fatty degeneration occurs, generally speaking, under the same conditions as cloudy swelling, with which it is closely related and often associated. It appears in the form of minute droplets and particles of fat in the interior of the cell, the protoplasm of which is clouded and granular. Later in the process larger globules of fat may form. The fat appears under the microscope as colorless, glistening, refractile particles and droplets with dark outlines; it is insoluble in acetic acid, but soluble in ether and alcohol, and stains black with osmic acid (Figs. 28 and 29). When the process has developed to a marked degree it gives the tissues an opaque, grayish, yellowish-white or yellow appearance that is either uniformly or irregularly distributed. When advanced it leads to disintegration of the cells into fatty and albuminous molecules—fatty necrobiosis—and may result, after removal of the detritus, in a marked diminution in size of the affected organ. But within limits this retrogressive process is also compatible with a certain degree of function and with complete “*restitutio ad integrum*,” in which case the fat is either oxidized or taken away and redeposited in the usual fat depots.

So-called fatty degeneration—degenerative lipogenesis—is generally regarded as a disintegration of the protoplasm of cells into fat. The fat is thought to be produced at the direct expense of the cell protoplasm, and not, as in fatty infiltration, from the constituents of the food. Bauer's experiments illustrate well the metamorphosis of protoplasm into fat. Bauer produced the highest degree of fatty accumulation in the protoplasm of the cells by phosphorus-poisoning in dogs that had lost all their fats through a long period of starvation. Taylor¹ has recently pointed out that, from the chemical point of view, it has not yet been satisfactorily demonstrated that fat is ever formed from cellular proteid. The fact that in fatty degeneration the cells suffer marked protoplasmic and nuclear lesions is regarded by Lindemann² and others as good evidence of the origin of fat from the cell protoplasm. Granted that fat forms in degenerated cells, it can still be urged that it is produced from carbonaceous compounds in the cells. This holds true also in regard to the development of fat in epithelial cells after death (Wentscher, Lindemann, and others). The question is an open one. It is important to bear in mind that fatty degeneration is associated with histologic changes in the cells; whereas fatty infiltration (page 100) corresponds with physiologic lipogenesis, and the cells suffer no other changes than those of pressure. For the present the term fatty degeneration should be used rather in the sense of cell degeneration associated with the formation of fat than of cell degeneration into fat.

Degeneration with the formation of fat occurs especially in the cells of the parenchymatous organs; but it may like cloudy swelling attack almost any kind of cell, inclusive of the ganglion-cells of the nervous system.

The concurrence of cloudy swelling and degenerative lipogenesis indicates that these changes are due to essentially the same causes. The formation of fat represents a more advanced stage of the degeneration than cloudy swelling, and is the result of a longer continuance or of a greater intensity of action of the special cause at work. The changes depend upon disturbances of cellular metabolism; they occur particularly in connection with local and general anemia. When a tissue, as, for instance, the heart muscle, receives a diminished quantity of blood on account of narrowing of the lumen of the arteries, due to thrombosis, embolism, or diseases accompanied by thickening of the intima, albuminous and fatty changes usually result. And in the case of the general anemias—secondary anemia, pernicious anemia, or leukemia—it is usual to find an extensively distributed degeneration with fat-production in the liver, the kidneys, the heart, and the skeletal muscles. In these and similar local and general conditions a lasting diminution in the supply of oxygen exists—there is not enough oxygen and other nutritive material to maintain the function of the cells. In actual starvation there is first absorption of all the fat in the body, accompanied by a marked diminution in the volume of many organs, and in the later stages albuminous and fatty disintegration of the kidneys, the liver, and other tissues.

The albuminous and fatty changes that occur in febrile diseases are regarded by some as due, in a certain measure, to the functional increase necessary to the production of the greater heat, especially as regards the organs that are the most important sources of heat, namely, the heart and liver. In febrile diseases, however, the direct action of the poisonous

¹ *Am. Jour. Med. Sci.*, cxviii., 1899; *Jour. Exper. Med.*, iv., 1899.

² *Ziegler's Beiträge*, xxv., 1899.

products produced by the bacteria and by the diseased body enter also into action.

Albuminous and fatty degenerations occur in practically all general infectious diseases, and in a large number of intoxications with various substances, such as phosphorus, arsenic, iodoform, chloroform, sulphuric and nitric acids, alcohol, carbonic oxid, and many bacterial products. In some of these instances of fatty and albuminous changes the precise cause of the degeneration must be sought in abnormal metabolism, due to the direct action of poisons which disturb the normal processes of oxidation. The changes at times occur to a more marked degree in certain localities than in others; this irregular distribution is attributable to the accumulation of the poisons in the organs specially affected. The production of the degenerations in some of these cases, as in the infectious diseases, may be aided to a great extent by diminution in the amount of oxygen taken in and by the action of the fever, as was mentioned above. Many of the substances named, as well as bacterial poisons and the toxic products produced in diseased organs, are eliminated by the kidneys and the liver, and here may be found an explanation of the extensive changes observed in the cells of these organs.

Virchow¹ regarded cloudy swelling as an anomaly of nutrition of a progressive character, believing that under the influence of the so-called inflammatory stimulus the cells absorbed so much nourishment that their structure became more or less disordered. It is hardly necessary to point out that microscopic appearances, the association with fatty degeneration, the frequent termination of the process in disintegration, and the absence of karyokinesis, all demonstrate that cloudy swelling is a change of retrogressive tendency.

Glycogenic Infiltration.—Glycogen is a carbohydrate formed in the body from the food and readily convertible into sugar. It is found in the tissues either in solution or in the form of hyaline, oval flakes, granules, or drop-like masses, lying in the cells or in the intercellular substance. It is easily soluble in water, especially when found in the liver, kidneys, and muscles; while that found in cartilage cells and surface epithelium is dissolved with some difficulty. It is readily demonstrated in the tissues because of its microchemical reaction with iodine, which stains glycogen a brownish-red. It is distinguished from amyloid material by not giving the reaction with iodine and sulphuric acid, and by being soluble in water. On account of its solubility in water the iodine is best applied in the form of an iodinized solution of gum arabic (Ehrlich)² or of a mixture of iodine and glycerin (Barfurth). According to Langhans,³ pieces may be fixed in absolute alcohol, cut into sections, and stained with a mixture of tincture of iodine, 1 part, and absolute alcohol, 4 parts. Only tissues removed and fixed immediately after death are suitable for the demonstration of glycogen, because postmortem it quickly changes into sugar.

Glycogen is found normally in the liver, in the epithelium of the uterus, in the skeletal muscles and the heart muscle, in the blood-serum, in leukocytes, in cartilage cells, and in most of the organs of the embryo. The quantity of glycogen in the liver decreases during starvation.

Under pathologic conditions glycogen is found in certain tumors, such

¹ *Virchow's Archiv*, viii., 1855.

² *Zeits. f. klin. Med.*, vi., 1883.

³ *Virchow's Archiv*, cxx., 1890.

as those of the testicle, bones, cartilages, muscles, in tumors of the kidney from adrenal rests, and of the cervical portion of the uterus. This occurrence of glycogen in tumors is interesting in view of the richness of embryonal tissues in glycogen, and the theory that the tumors spring from embryonal remnants (Cohnheim) would seem to receive some support from this fact. Glycogen is also found in pus-corpuses; and Czerny observed that the leukocytes give the glycogen reaction in conditions characterized by cachexia.

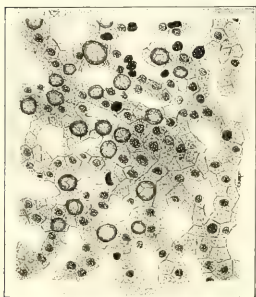


FIG. 30.—Glycogenic infiltration of the liver. $\times 300$.

Glycogenic infiltration is especially marked in diabetes mellitus (Ehrlich). While a large part of the excessive amount of sugar formed in this disease is eliminated in the urine, glycogen is also produced in large quantities, and is found in abnormal amount in the leukocytes and the plasma of the blood, in the liver (Fig. 30), in the kidneys, especially in the epithelial cells lining the loops of Henle, and elsewhere. Experimental diabetes produced by extirpation of the pancreas (Minkowski) has been shown by Trambusti¹ to be followed by a marked glycogenic infiltration of the kidney, liver, and the leukocytes.

Fatty Infiltration; Lipomatosis.—Normally fat is found in various parts of the body, being stored in the cells pending the need of the organism for the potential energy the fat contains, and which, when required, is liberated by oxidation of the fat. The quantity of fat in storage will vary according to the amount of fat produced in the processes of nutrition and metabolism, and the amount consumed in the processes of katabolism. The fat represents in part fat brought as such into the body in the food, emulsified and absorbed in the chyme, and carried by the blood, either in solution or suspended as fine particles, to the storage depots in the cells; in part it represents fat produced by cellular activity from the albuminous and carbohydrate constituents of the food. When an excessive amount of fat is produced, or when the quantity consumed is exceedingly small, or when both of these contingencies concur, a superabundance of fat results, which, if it passes beyond certain limits, becomes abnormal, and conditions develop that are known as obesity, adiposity, polysarcia, or lipomatosis.

The processes that lead to these conditions are referred to as fatty infiltration, and are of a different nature from those concerned in other fatty changes.

As already indicated, fatty infiltration occurs in obedience to the same general laws that govern the physiologic storage of fat, the difference being largely one of degree. Thus, an excessive amount of fat may be produced when the diet contains, in addition to the usual amount of proteids and carbohydrates, an inordinate amount of fat; some of the fat is then, in all probability, simply absorbed from the digestive tract and carried in solution or suspension in the blood to the places of deposit. Or, as is more likely, stored fat results from metabolism of the proteids and carbohydrates, while the fat in the food is immediately oxidized. In this latter case the cell acts

¹ *Centralb. f. allg. Path. u. path. Anat.*, iii., 1892.

as a retort in which the albuminous and starchy substances are converted into fat. The fat is, however, not produced at the expense of the protoplasm of the cell itself, but only from substances brought to it.

In addition to the storage of fat through excessive production from the food, certain conditions that lead to diminished consumption of fat are to be considered. Here are included all those states characterized by lessened labor on the part of the cells, such as absence of muscular activity, sluggish respiration, and chronic anemia, leading to a scant supply of oxygen.

Then there are conditions in which, with a normal supply of food, the constituents of the diet being correctly balanced, and in which the general processes of oxidation seem to be at par, there is, nevertheless, an excessive local or general accumulation of fat. Such conditions depend upon anomalous metabolic processes of unknown origin, the tendency to which may be acquired or inherited. These states seem to depend to a certain extent upon a local or general diminution in the energy or activity of the cells (Cohnheim). The progressive character of the disturbed metabolism is often marked. Among the instances in which this tendency to excessive fatty deposition



FIG. 31.—Fatty infiltration of heart muscle. The fat is stained orange with sudan III. The muscle fibers are compressed.

seems to be acquired may be mentioned the obesity of eunuchs, and of women after premature or natural menopause.

From these general etiologic considerations it becomes possible to define fatty infiltration as the storing of fat in the protoplasm of cells without any essential change in their structure, the fat being in part due to increased formation by the cells, in part to increased supply.

Fatty infiltration may be *general* in the form of a general obesity or universal lipomatosis. Here the increased deposition of fat occurs first in the subcutaneous and subserous connective tissue, in the liver, and in bone-marrow—places where fat is normally stored, and then in places where fat does not occur under normal conditions, namely, in the intermuscular connective tissue of the heart (Fig. 31) and the skeletal muscles, in some cases in submucous connective tissue and elsewhere. In these cases there is often a very marked individual predisposition.

A *local*, circumscribed lipomatosis also occurs. This is commonly seen as a marked increase of fat around atrophic organs or organs diminished in size from other causes; as, for instance, around contracted kidneys and

between the narrow fibers of the atrophic heart, and in the skeletal muscles in the disease known as pseudohypertrophic muscular paralysis. Particularly in the latter it would seem that peculiarities in cellular activity form the predisposing causes for the excessive deposition of fat, which here exceeds the mere filling up of the space left by the atrophic muscle fibers. In connection with this, reference may be made to the so-called multiple symmetric lipomas—multiple, circumscribed, symmetrically disposed, fatty overgrowths—the development of which must be ascribed to peculiarities in cellular activity.

Functional disturbances may result from fatty infiltration, as, for example, in the case of the liver, and particularly of the heart, where the deposition of fat between the muscle fibers may result in muscular insufficiency, and even in rupture of the wall when the latter has become so infiltrated with fat that it no longer possesses the necessary degree of resistance to the intracardiac pressure. An excessive universal lipomatosis may also reach such an enormous extent as to interfere with the movement of the body and with the performance of other functions. In some of the cases of great obesity the thyroid gland has been found diseased.

As stated in the definition of fatty infiltration, there is an absence of all structural changes in the affected cells other than those due to the mere presence of the fat. In the liver cells the beginning of fatty infiltration is signaled by the presence of numerous small fat drops, but there is no marked disturbance in the protoplasm of the cell. Later on, the droplets coalesce to form larger globules, so that in advanced cases the protoplasm forms a capsule for the fat globule, and in this membrane the nucleus will be found crowded to one side, giving rise to the so-called seal-ring appearance (Fig. 32). In

the connective-tissue cells the fat also appears as small drops which rapidly coalesce, so that a large globule is formed, which presses the nucleus to one side.

The differential microscopic diagnosis of fatty infiltration and other fatty processes rests essentially upon the presence in the cells, in the latter case, of changes that are indicative of disintegration of the protoplasm (page 97); whereas the cell of fatty infiltration is normal except for the presence of fat. Usually the infiltrated fat occurs in much larger drops than fat under other circumstances, but not invariably. The occurrence of fat in places in which it is not found normally, as, for instance, in the



FIG. 32.—Fatty infiltration of the liver. Large fat globules occupy the liver cells and crowd the nuclei to one side. $\times 125$.

muscular fibers of the heart or skeletal muscles, in glia cells, etc., speaks in favor of more deep-seated changes. When the fatty infiltration recedes, then the large fat globules become smaller and divide into minute droplets that are gradually removed, so that the cells again present their usual appearance.

In the connective tissue and the bone-marrow disappearance of the fat, both after excessive infiltration as well as under normal conditions, may be followed by the infiltration of serum into the tissue, which becomes jelly-like and translucent, a condition described as serous atrophy of adipose tissue.

Pathologic Pigmentation.—Abnormal pigmentation of tissues may occur in various ways. It may be due to an excessive pathologic formation of the pigment normally found in the skin and elsewhere—*autochthonous* or *metabolic pigmentation*; or it may follow changes in the hemoglobin of the red blood-corpuscles—*hematogenous pigmentation*; or it may be due to absorption of the pigment found in the secretion of the liver, the bile—*biliary pigmentation*, icterus, or jaundice. Finally the pigment particles may be imported into the body from without by inhalation through the lungs, through wounds (as in tattooing), or by introduction into the stomach.

Pigmentation as a whole includes many different and complex processes. In some cases the pigment is the product of increased cellular activity, and the pigmentation bears the stamp of a progressive rather than a regressive disturbance, as, for instance, in the formation of pigment in melanotic tumors. A number of pigments are produced by physiologic as well as pathologic changes in the hemoglobin of the blood. The biliary pigment is a physiologic derivative of hemoglobin; and biliary pigmentation, or jaundice, usually depends upon mechanic obstruction to the outflow of the bile, although in some instances the process is different and more complex. The so-called hematogenous pigments are due to pathologic changes in the red blood-corpuscles, and the pigmentation with these substances is usually a part of secondary absorptive and eliminative processes. Pigmentation with pigment introduced from without is a pure infiltration.

Metabolic Pigmentation.—Pigment normally occurs in various parts of the body in the form of yellowish, brown, or black granules, lying chiefly in the cells, but also in the intercellular substance. Such pigment is found in the deeper layers of the rete Malpighii of the skin, in the epithelium of the retina, in the hair, and in the ganglion cells of the nervous system. Furthermore, pigment is found in the connective tissue of the pia mater, in the choroid and sclerotic coats of the eye, in the muscle cells of the heart, in the adrenals, the testicles, the kidneys, the liver, and in the smooth muscle fibers of the small intestine of older persons. The iron reaction of the pigment in the liver and the testicles speaks in favor of its hematogenous origin. These pigments are called by various names, such as melanin, lipochrome, and hemofuscin.

This normal pigmentation may increase under various physiologic and morbid conditions. The pigmentation in the skin is usually greatly increased during pregnancy; the formation known as freckles is also due to localized increase of pigmentation in the skin. In Addison's disease an excessive pigmentation of the skin develops, due to increase of the normal pigment (Fig. 33, B). A marked increase in the pigmentation of the ganglion cells is usually regarded as of pathologic import. The greatest degree of pigment formation occurs in the so-called pigment moles of the skin and in melanotic tumors.

In the last-named growths the cells (Fig. 33, A) may be diffusely pigmented with brownish or blackish granules, which also lie in the intercellular substance, so that the growth may be entirely black, and the fluid that exudes as black as ink. The urine in these cases may contain substances which on exposure to the air become changed into black pigment particles (melanuria).

The yellowish, brownish, or black granular pigment found under the various conditions mentioned is usually regarded as the product of a special

cellular activity. As regards the skin, Kölliker believes that the pigment is brought by wandering connective-tissue cells—*chromatophores*—which send processes between and even into the epithelial cells, and that in this manner transfer of pigment is accomplished. Karg transplanted a piece of white skin upon an ulcer of the leg of a negro, and found that the originally white skin became black, due to the appearance of pigmented connective-tissue cells between the epithelial cells and the transfer of the pigment to the latter. The origin of the pigment-carrying wandering cells is obscure. Concerning the exact manner of formation of the pigment in other places nothing definite is known. Nor is it known from what material the pigment is formed; whether from the coloring-matter of the blood—which does not



FIG. 33.—Various kinds of pigmented cells: *A*, cells containing melanin, from a melanosarcoma of the choroid; *B*, pigmented cells from the skin in Addison's disease; *C*, cells filled with coal-dust in the alveoli of the lung; *D*, cells containing changed red cells and blood pigment in lung the seat of passive congestion. $\times 650$.

seem likely, because there is nothing to indicate its formation in the vicinity of the blood-vessels—or from albuminous substances. The large amount of sulphur in some of these pigments (von Nenski)¹ favors the view that it is elaborated by the cells from albuminous material.

Certain pigments of a different composition and of obscure origin are found in the corpus luteum of the ovary in the form of a yellow pigmented fat, called lutein, and in certain rare lymphomatous tumors, called chloroma, on account of their presenting a more or less distinct green color, which also seems to depend upon the presence of a pigmented fat; the yellow formations in the skin known as xanthoma also contain a granular pigment that belongs to the lipochromes. Virchow, and later Böstrom, Hanseemann,

¹ *Arch. f. exp. Path.*, xx., 1886.

and Heile,¹ have each described cases in which all the cartilages of the body, as well as other structures, were black, due to the presence of a brownish or black iron-free pigment. This condition is known as *ochronosis*; its cause is not known. Formalin, according to Heile, produces a similar pigmentation of cartilage. Von Recklinghausen regards the yellow iron-free pigment (hemofuscin) of the smooth muscle fibers of the small intestine, seen especially in drinkers, and of other muscular organs, as a derivative of hemoglobin.

Absence of pigment may be congenital; it may be universal (*albinismus universalis*) or partial (*albinismus partialis*). Acquired absence of pigment is discussed in the part devoted to the Pathologic Anatomy of the Skin.

Hematogenous Pigmentation.—This form of pigmentation depends upon the deposition in the tissues of pigment derived from hemoglobin. It occurs either as a secondary process after hemorrhages and thrombosis, or as the result of solution of hemoglobin in the blood-plasma and the formation of granular pigment in the circulating blood.

In the first instance the pigmentation is the result of physical and chemical changes in the hemoglobin, incidental to the absorption and removal of disintegrating red blood-corpuscles and other detritus. The various changes in the color of cutaneous extravasations, as, for instance, in a "black eye," which becomes brown, bluish-green, and yellow before all traces disappear, are the external indications of the various stages in the process of absorption. Similar color changes are observed in connection with the absorption of internal hemorrhages, as in the brain.

After an extravasation of blood the red blood-corpuscles undergo the following changes: A part is returned to the circulation unaltered, by way of the lymphatics; another part loses its hemoglobin, which is dissolved by the serum and diffused throughout the tissues, which it stains brownish or reddish, while the albuminous stroma of the red cells falls to pieces; a third part of the red corpuscles disintegrates, while still containing hemoglobin, into brownish or reddish particles or fragments. Some of the dissolved hemoglobin is absorbed and eliminated in the urine as methemoglobin or urobilin; the remainder of free hemoglobin, as well as that contained in the disintegrating red corpuscles, undergoes further chemical changes whereby it is converted partly into hematoidin, partly into hemosiderin.

In tissues hardened in alcohol for microscopic purposes the hemoglobin in extravasations may form long, red, splinter-like crystals. These crystals are composed of parahemoglobin, an insoluble form of hemoglobin which develops under the influence of alcohol.

Hematoidin is a pigment derived from hemoglobin, and occurs either in the form of yellowish or brownish granular masses, or as brick-red rhombic or needle-shaped crystals. It is nearly, if not quite, identical in chemical composition with bilirubin, and responds to Gmelin's test (Virchow); it does not contain iron, and is insoluble in water, ether, and alcohol, but soluble in chloroform and alkaline fluids. It is formed more especially in large extravasations and in hemorrhages into preformed cavities, where the blood is not so much exposed to the action of living cells (Quincke)² and where there is a lack of oxygen (Thoma and Panski).³

¹ Virchow's *Archiv*, clx., 1900.

² *Deutsch. Arch. f. klin. Med.*, 25, 27, and 33.

³ *Arch. f. exp. Path.*, xxxi., 1893.

Hemosiderin appears in yellowish-brown or brown granules and granular heaps, which are usually enclosed in cells (Fig. 34), but may lie free in the tissue-spaces. It is insoluble in water, and contains iron. If a microscopic section containing hemosiderin is treated with a solution of potassium ferro-

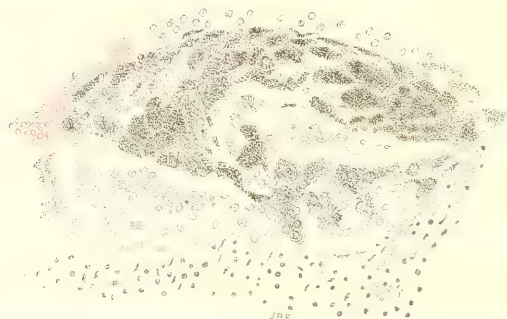


FIG. 34.—Hemorrhagic cyst in the pineal gland. There are masses of brownish granular pigment, and many cells are filled with this material (hemosiderin). To the left are some unchanged red cells. Hematoxylin and eosin. $\times 125$.

cyanid and hydrochloric acid, the hemosiderin granules are stained blue, owing to the formation of Prussian blue (Fig. 35); under the influence of ammonium sulphid or hydrogen sulphid the granules become black, on account of the formation of ferrous sulphid.

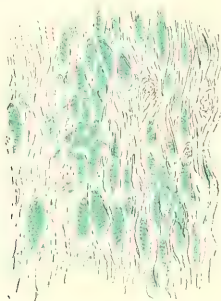


FIG. 35.—Masses of hemosiderin in the thickened endocardium beneath an old thrombus. The blue iron reaction was obtained by treating the sections with potassium ferrocyanid and hydrochloric acid. $\times 125$.

Hemosiderin is formed when the extravasated blood is exposed to the action of living cells and of oxygen. The pigment is consequently found by preference in smaller extravasations and at the periphery of larger ones, in small thrombi, and in chronic passive hyperemia of the lungs and other organs, accompanied with hemorrhage by diapedesis. The section

from which the drawing reproduced in Fig. 35 was made came from the wall of a right ventricle, upon the endocardium of which an old thrombus was situated.

While these changes are taking place in the dissolved hemoglobin, as well as in that attached to fragments of red blood-corpuscles, the so-called pigment-carrier cells (Fig. 33, *D*) are transporting the fragments and detritus to the surrounding tissues, and by way of the lymphatics into the regional lymph-glands, which become more or less pigmented. These carrying cells are chiefly leukocytes which have taken up into their interior not only hemosiderin and hematoidin granules, but also fragments of or entire red blood-corpuscles, the pigment of which may undergo further changes in the interior of the carrier cells. The protoplasm of these cells may be stained a diffuse yellow by the dissolved hemoglobin. In this way the changes of color in the vicinity of extravasations and in the extravasated blood itself are explained; as hemosiderin and hematoidin are formed the color becomes more yellowish. Hematoidin may to a certain extent be dissolved by the alkaline fluids, and hemosiderin is probably also gradually destroyed or removed; it may lose its iron, and may be changed to a colorless substance. Hematoidin entering the blood is secreted by the liver as bilirubin, with which it is said to be identical in composition; it is finally eliminated by the kidneys as urobilin.

Pathologic hematogenous pigmentation also occurs after the extensive destruction of red corpuscles in the circulating blood and the setting free of hemoglobin in the plasma. Pigmentation of the internal organs (liver, spleen, marrow of bones) due to the deposition of hemosiderin—*hemosiderosis*—undoubtedly occurs to a limited extent physiologically as red blood-corpuscles gradually wear out and are destroyed.

Excessive destruction of the red cells in the blood occurs in septic infections, grave malarial fever, pernicious anemia, and in many forms of intoxication, as, for instance, with potassium chlorate, poisonous fungi, toluyendiamin, etc.; in the disease known as periodic hemoglobinuria, and after the introduction of the blood of one animal into the body of another of a different species. The general results that may follow such excessive disintegration of red blood-cells are: *hemoglobinemia*—i. e., a discoloration of the plasma by the hemoglobin in solution; *hemoglobinuria*, or *methemoglobinuria*, when the dissolved hemoglobin is eliminated in the urine, which then becomes brownish-red or dark red in color; increase in the amount of pigment in the bile; and pigmentation of various internal organs by pigments derived from hemoglobin, especially by hemosiderin.

The degree of the pigmentation of the internal organs depends upon the relation of the pigment set free in the blood to the capacity of the liver to convert it into biliary coloring-matter. If the liver is not able to utilize, in the formation of biliary pigments, all the blood-pigment brought to it, then the derivatives of the hemoglobin are deposited in various internal organs, and to a certain extent are excreted in the urine. The pigmentation produced in this manner is due chiefly to the deposition of hemosiderin; the iron-free hematoidin does not seem to be produced to any great extent, or, if so, it is largely utilized by the liver (bilirubin). The iron-containing pigment is deposited in the form of yellow or brown granules or flakes in the liver, spleen, bone-marrow, lymph-glands, and kidneys. The pigment particles are brought to the organs in question either free or enclosed in leuko-

cytes; thence they are taken up by the endothelial cells of the capillaries and passed into the cells proper of the organs. In pernicious anemia and in malaria the pigmentary infiltration of the liver cells may be so great as to give the organ a yellowish-brown, orange, or bluish color, which is best marked in the periportal connective tissue and in the periphery of the acini. In the lymph-glands the particles are found especially in the free cells; in the spleen the free as well as the fixed cells may become pigmented; and in the bone-marrow the pigment is partly enclosed in cells lying in the capillaries, partly in the endothelial cells, and also in the marrow cells proper. In the kidneys the pigment particles are to be found in the endothelial cells, the epithelium of the convoluted tubules, and in the lumen of the tubules. In malaria, in addition to the hemosiderin produced by the disintegration of the red cells, the parasites elaborate a black iron-free pigment, which is deposited in various organs, and is the essential cause of the melanosis or

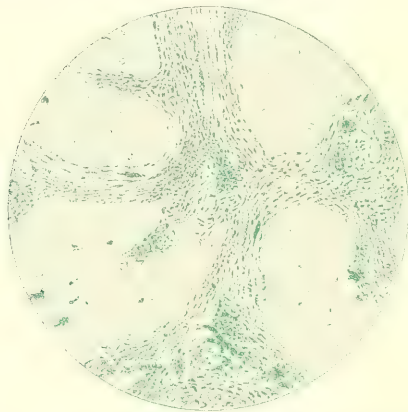


FIG. 36.—Hemochromatosis and cirrhosis of the liver. Iron reaction with potassium ferrocyanid and hydrochloric acid. $\times 100$.

pigmentation of the spleen, liver, bone-marrow, and brain-cortex observed in chronic malaria.

Under the name *hemochromatosis* von Recklinghausen described a general pigmentation with an iron-containing and an iron-free pigment. This form of pigmentation is associated with cirrhosis of the liver and of the pancreas, and at times with diabetes mellitus (the so-called bronzed diabetes) (Fig. 36). The ordinary destruction of red blood-corpuscles does not produce such widespread and general pigmentary deposits.¹

Pseudomelanosis is the term applied to a certain bluish-gray or black discoloration that is found in the peritoneum and the abdominal organs of cadavers. It has been regarded as entirely of postmortem origin, but, according to Neumann, it depends upon local conditions existing during life which favor the development of hemosiderin, the subsequent combination of which with ammonium sulphid gives rise to the discoloration.

¹ See Opie, *Jour. Exper. Med.*, iv., 1899.

The green discoloration that forms along the subcutaneous blood-vessels during decomposition is due to the action of hydrogen sulphid upon methemoglobin.

Biliary Pigmentation.—Icterus, or jaundice, is a general pigmentation of the tissues of the body with the coloring-matters of the bile. The biliary pigments are produced in the liver. This is shown by the facts that neither the blood of the portal vein nor that of the hepatic artery contains any of the constituents of the bile, and that when the liver is removed from geese and ducks no bile is produced (Minkowski and Naunyn). The biliary pigments are derivatives of hemoglobin, and the biliary pigment known as bilirubin is identical with hematoidin, the iron-free derivative of hemoglobin found in extravasated blood. Under normal conditions the biliary pigments are passed on into the intestines, together with the other constituents of the bile, a part being evacuated with the feces, while another part is absorbed into the blood through the mucous membrane of the intestine (Hoppe-Seyler). When it reaches the blood it has undergone such chemical changes as to elude demonstration, but its presence in the blood in some form is shown by the constant occurrence in the urine of a derivative of bilirubin known as urobilin.

Icterus is produced by the passage of the bile and its coloring-matter from the liver into the lymphatic vessels and the blood. The essential cause of icterus is *obstruction to the outflow of the bile into the intestines*. Among the many conditions that may give rise to biliary obstruction are catarrhal inflammation of the bile-ducts, and the occlusion of the lumen of the biliary papilla in the duodenum by a plug of mucus; narrowing and closure of the biliary passages by impacted calculi, contracting scars, and tumors; fibrous bands causing kinking of the ducts; pressure of enlarged lymph-glands; inflammatory foci, connective-tissue proliferation, and tumors developing in the liver-substance and compressing or obliterating the biliary canals and capillaries so as to prevent the outflow of the bile.

The typical results of such obstruction are the following: No more bile reaches the intestine, the contents of which lose the color due to the bile and become clay-colored; intestinal digestion is disturbed and putrefactive processes develop on account of the absence of bile. The damming of the bile causes dilatation of the biliary ducts and canals, stagnation of their contents, and absorption by the lymphatics of the biliary coloring-matter and acids, which reach the general circulation by way of the thoracic duct; the intercellular biliary capillaries as well as the intracellular passages are distended, and the liver-cells themselves become pigmented because they cannot get rid of the pigment produced in their interior. Excessive dilatation of the biliary capillaries may lead to their rupture and the direct entrance of bile into the circulation (Ziegler). Some authors, as Szubinski,¹ claim that there are two sets of passages in the liver-cells—biliary and vascular—so that the bile is readily absorbed into the blood in stagnation in the intracellular biliary canals. A general staining of the organs and fluids of the body by the biliary coloring-matter present in the blood, either in solution or as granular pigment particles, is produced. During life this is best shown by the yellow or greenish-yellow discoloration of the skin, the conjunctivæ, and the urine; after death the internal organs, the serous mem-

¹ Ziegler's *Beiträge*, xxvi., 1899. See also Nauwerck, *Münch. med. Woch.*, 1897; and Fütterer, *Medicine*, 1897.

branes, the blood-plasma, transudates and exudates that may be present, are all found more or less bile-stained. The solid pigment particles which circulate in the blood, either free or enclosed in leukocytes, are deposited here and there in the body, especially in the lymph-glands, spleen, and bone-marrow. In persistent and excessive icterus many of the tissues may contain bilirubin in solid form, usually as granular particles, rarely in the shape of rhombic and needle-shaped crystals. The kidneys, which eliminate the biliary coloring matter, show pigmentation of the epithelial cells of the uriniferous tubules, and of the casts that are usually present in the tubules in jaundice.

The general functional disturbances characteristic of icterus depend not so much upon the presence of the biliary coloring-matter in the circulation as upon the simultaneous presence of the biliary acids. These acids have the power of destroying the red blood-corpuscles, thus setting free hemoglobin (Leyden,¹ Löwit²). The free hemoglobin increases the formation of bilirubin by the liver, and in this way it may serve to intensify the jaundice at the same time as the iron-containing pigment derived from the hemoglobin—hemosiderin—is deposited in the various internal pigment depots.

The removal of the biliary obstruction is succeeded by a gradual disappearance of the pigmentation. The liver secretes a larger amount of bile, which is to a great extent excreted by the intestines, and as the jaundice disappears the amount of urobilin in the urine is also greatly increased.

More or less well-marked icteric pigmentation is met with in conditions in which the red corpuscles are destroyed in the circulating blood. This occurs in many infections and intoxications; in septicemia, typhoid fever, yellow fever; after the bite of venomous serpents, blood-transfusion, inhalation of chloroform and ether, the administration of toluyldiamin, etc. It was formerly held that in these cases the formation of the biliary pigment, the bilirubin, occurred in the blood, and the jaundice was designated as hematogenous, in distinction from the jaundice produced by biliary obstruction, which was termed hepatogenous. This can no longer be regarded as correct. On removing the liver from geese and ducks, Minkowski and Naunyn found that the production of bile ceased. They then caused extensive destruction of the red corpuscles by allowing the animals to inhale arsenous hydrid; but even then no biliary pigment was formed, showing conclusively that the liver is the seat of production of the biliary coloring matter. It must again be stated, however, that bilirubin, or hematoidin, is formed in blood-clots, and the yellow color that occurs in the process of absorption may be considered a local icterus in so far as the yellow color depends upon the presence of hematoidin; but biliary pigment is never formed outside the liver to the extent that a general jaundice is produced. The so-called toxic or infectious icterus depends upon an increased production of biliary pigment in the liver and the absorption of the bile into the circulation. The causes that determine the absorption of the bile under these circumstances are not clearly understood; it is believed that it may occur from the biliary passages and from the intestines, and that the changes in the consistency of the bile, due to the increased amount of pigment, favor absorption (Stadelmann).³

¹ *Pathologie des Icterus*, 1866.

² *Ziegler's Beiträge*, iv., 1889.

³ *Der Icterus*, 1891.

Another circumstance that shows toxic or infectious icterus to be hepatogenous is the fact that the urine and the blood may contain biliary acids.

An excessive destruction of red blood-corpuscles in the circulating blood under toxic or infectious influences results, then, in an increased formation of bilirubin by the liver from the liberated hemoglobin, which may be absorbed into the circulation and give rise to jaundice, while the derivatives of hemoglobin retained in the organs consist almost entirely of hemosiderin.

The so-called *icterus neonatorum*, or jaundice of the newborn, has been explained in a variety of ways. In many cases it is due to obstruction of the biliary ducts. Thus, in hereditary syphilis Gerhardt and Somer found the jaundice to be dependent on connective-tissue growth around the bile-passages, which were compressed. In another group of cases the jaundice has an infectious basis, due to septicopyemic processes.

In a large number of instances, however, jaundice develops in healthy children during the first few days after birth. This is *icterus neonatorum* in the strict sense. Frerichs¹ explained it as due to a fall of pressure in the capillaries of the liver, which resulted in an entrance of bile into the blood. Others have advanced the view that the increased destruction of red blood-corpuscles causes an excessive production of bilirubin, which is absorbed. Hewitt and Silbermann regard the icterus as dependent upon an increased destruction of red corpuscles and upon biliary obstruction due to compression of the bile-capillaries by the dilatation of the blood-vessels of the liver that occurs after birth. Birch-Hirschfeld² regards the jaundice as due to compression of the biliary capillaries and passages by Glisson's capsule, which follows the venous congestion that at times occurs during and after birth. The resulting edema of Glisson's capsule, which is often demonstrable, develops especially after protracted labor, in cases of twists of the umbilical cord, and in insufficient heart action. Ziegler believes that the jaundice depends upon resorption of the biliary pigment, which is not only produced in large quantities in the liver, but is also absorbed in large amount from the meconium and carried back to the liver.

The jaundice of the newborn is characterized not only by a diffuse yellow pigmentation of the tissues, but also by the deposit of bilirubin in adipose and connective tissue.

Imported, or External, Pigment.—Pigmentation of external origin may take place :

a. Through the skin ; and here most frequently as the result of tattooing. This practice consists of puncturing the skin with a sharp instrument and then rubbing in various insoluble, granular coloring matters, such as India ink, charcoal, cinnabar, etc. A part of the material remains in the small cicatrices that form, while some is carried by the lymphatics to the regional lymph-glands, which also become pigmented.

A similar traumatic pigmentation of the skin of the face and elsewhere occurs after explosions of gunpowder, leading to the formation of powder-marks ; also in coal-miners from the entrance of coal-dust into the skin. A permanent local pigmentation of the skin occurs in workers with silver.

b. Through the Alimentary Canal.—The only important form of pigmentation due to introduction by way of the stomach is pigmentation by silver—*argyrosis*, or *argyria*. When preparations of silver are administered for a

¹ *Leberkrankheiten*, i., 1858.

² *Virchow's Archiv*, lxxxvii., 1882.

long time the silver is absorbed into the circulation, presumably as an albuminate, and is deposited in the form of black or brown granules in various tissues, which become uniformly dark gray in color. The deposition takes place chiefly in the skin; in the kidneys, where it is deposited in the intercellular substance of the glomeruli and the medullary pyramids; in the arterial intima, the serous membranes, the choroid plexuses of the brain,¹ etc. The blue line along the gums in lead-poisoning (saturnism) is due to the ingestion of lead with the food.

c. *By Inhalation.*—The lung is the most frequent seat of pigmentation. Finely divided dust carried into the lungs in inspiration is in part retained. The most frequent pigment thus introduced is coal-dust. Residents of large cities, as well as miners and workers in coal, always present more or less coal-dust pigmentation, or anthracosis, of the lungs, and not infrequently this reaches such a degree that the organ becomes perfectly black. The coal-dust is at first free in the alveoli or enclosed in leukocytes and alveolar epithelial cells (dust-cells or carrier-cells) (Fig. 33, C). Later it is also found in the alveolar septa, and in the interlobular, perivascular, and peribronchial connect-

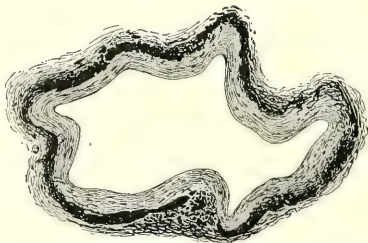


Fig. 37.—Masses of coal-dust in perivascular lymph-spaces of a pulmonary vein. $\times 75$.

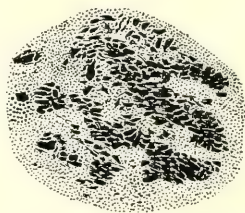


Fig. 38.—Coal-dust in peribronchial lymph-node. $\times 75$.

ive tissue, where the granules are deposited in compact masses (Fig. 37). From the lungs the pigment is carried by the lymph-current to the peribronchial lymph-glands (Fig. 38), which may become black throughout and considerably enlarged. On account of the mechanic irritation produced by the pigment connective-tissue proliferation may take place, resulting in the formation of a great deal of hard, fibrous tissue about the bronchi and blood-vessels, and between the lobules. When inflammatory or tuberculous foci are replaced by connective tissue this may become completely infiltrated with coal-dust, giving rise to black areas of induration. According to some authorities, however, the inflammatory changes following the inhalation of coal-dust are due to bacteria attached to the dust rather than to the mechanic action of the latter.

From the lungs the coal-dust may reach the general circulation, either directly by being deposited throughout the entire thickness of the walls of the vessels and thus becoming mixed with the blood (Arnold), or by the softening of anthracotic peribronchial lymph-glands and secondary involvement of the walls of the large veins in their neighborhood (Weigert).² The intima of these large veins often shows pigmentation. The coal-dust

¹ Von Kahlden, *Ziegler's Beiträge*, iv., 1894.

² *Fortschritte d. Med.*, 1883.

might also reach the general circulation by way of the lymphatics after passing the glandular filters, or by retrograde transport along mediastinal lymph-currents running in reversed direction to the normal. Coal-dust that has reached the general circulation is deposited in the liver, spleen, or bone-marrow, and an instance has been described by Welch in which it infiltrated the liver to such an extent as to be regarded as the cause of the cirrhosis that existed.

Iron workers and polishers occasionally present a reddish pigmentation of the lung, due to the inhalation of powdered oxid of iron; this is known as *siderosis* of the lung. *Chalcosis* and *silicosis* result from the inhalation of marble-dust¹ and quartz-dust respectively.

The Petrifying Infiltrations and the Formation of Calculi.—Petrifying infiltration is due to the deposition in the tissues of certain solid, crystalline, amorphous, or granular salts, which are either salts of lime or salts of uric acid. When the former are deposited the process is known as *calcareous infiltration*, or *calcification*.

Calcification is due to the precipitation in the tissues of granular particles and masses of the phosphates and carbonates of lime and magnesium. It takes place as a physiologic process in the calcification of osteoid tissue during the process of ossification of the skeleton; here calcification occurs as an essential step in the formation of the new tissue. With the further exception of the calcification in tumors that produce bone, all other instances of calcareous infiltration in the body must be regarded as retrogressive changes, because no new tissue is formed, but old tissue is petrified.

Pathologic calcification, or petrification, occurs almost without exception only in degenerating, dying, or dead tissue.

In old age calcification of the costal cartilages, of the cartilages of the larynx, and of the walls of arteries takes place with great constancy; it is believed to be due to an excessive quantity of lime salts dissolved in the blood in consequence of senile involutionary changes and processes of absorption in the bones. In this form of calcification, which is so constant as almost to be physiologic, the lime salts are deposited in the arterial walls and in the disintegrating intercellular substance of the cartilages—the antecedent retrogressive changes in these being also of constant occurrence in old age. It may occasionally happen that the increased resorption of lime salts leads to calcification of apparently normal tissue, such as the lungs, the kidneys, and the mucous membrane of the stomach. The resorption of lime salts from one tissue and their deposition in another are referred to as lime metastasis,² or metastatic calcification (Virchow).

While metastatic calcification is of frequent, almost constant, occurrence in old age, calcification of dead or dying tissue is also very often observed in early life, when the source of the lime salts must be sought in the food rather than in processes of reabsorption.

Calcification occurs very often in connective tissue the seat of sclerosis and hyaline degeneration, as, for instance, in the blood-vessels in arterio-sclerosis, in hyaline degeneration of small cerebral vessels, in the heart-valves in endocarditis, in chronic inflammatory thickenings in the pleura and pericardium, and in the thyroid gland. It also takes place in foci of

¹ Betts, *Jour. Am. Med. Assoc.*, xxxiv., 1900.

² Some writers object to this use of the word metastasis, the term really implying a transfer of disease.

fatty degenerations in the arterial walls, and in various tumors, as fibromyoma of the uterus, in all kinds of necrotic areas due to caseation or coagulation-necrosis, in inspissated pus and inflammatory exudates, in the capsules of animal parasites (trichina), in thrombi (phleboliths), and in dead fetuses retained in the peritoneal or uterine cavity (lithopedion). Calcareous infiltration also takes place in dead ganglion-cells of the brain in shock, softening, and other nervous diseases (Friedländer), and in the renal epithelium after necrosis following anemia (Litten, Israel), or in that caused by various forms of intoxication, such as with corrosive sublimate (Kaufmann) and with aloin (Gottschalk).

The exact chemical reactions of calcification are not known. In general it would seem to depend upon the precipitation of insoluble or very slightly soluble calcareous salts in organic substances that have great affinity for lime; and we may conclude, in view of the fact that necrotic foci nearly always become calcified, that calcification of degenerated or dead tissue occurs, as a general rule, when the blood contains an abundant amount of lime salts.

Calcareous infiltration produces more or less firm, whitish areas; at times compact masses of stony hardness are formed. In some places calcification results in the formation of round or oval concretions. Such concretions occur normally, in the form of laminated globular masses, in the pineal gland and in the plexuses of the cerebral ventricles, forming the so-called brain-sand (*acervulus cerebri*). They may occur in the cerebral membranes, in various tumors of these structures (*psammoma*), and also in caseous foci and hyaline connective tissue. The formation of such concretions depends upon the calcification of necrotic cells and intercellular substance.

Microscopically calcareous tissue may be recognized by the presence of fine, refractile granules in the intercellular substance or in the cells. These granules are dark in transmitted, white in reflected, light. Calcification in structureless necrotic masses gives rise to the formation of roundish and irregular granules, and occasionally to more homogeneous masses. Upon the addition of strong hydrochloric or nitric acid to calcareous material effervescence takes place, carbonic-acid gas being liberated in the form of bubbles. Tissues the seat of calcareous infiltration differ from normal tissue in their behavior to certain stains, inasmuch as they stain a diffuse bluish-violet with hematoxylin and red with picrocarmin.

A deposition in the tissues of the salts of *uric acid* occurs in the disease known as gout, which is characterized by a general disturbance of metabolism, in consequence of which an excessive amount of uric acid is formed and deposited in various parts of the body.

The infiltration affects by preference the articular cartilages and ligaments, the tendons and tendon-sheaths, the kidneys, the subcutaneous tissue, the auricular cartilages, etc. The favorite seat for the deposit is the metatarsophalangeal joint of the big toe, where it occurs during the acute attack of gout. The material deposited consists of the salts of uric acid, especially sodium urate, accompanied by smaller amounts of phosphate and carbonate of lime. The sodium urate appears in the form of sheaves of fine, needle-shaped crystals, which are first deposited in the intercellular substance of the cartilages, the cells of which are at first unchanged. As the infiltration increases the cartilage becomes opaque and dark in transmitted light; soon extensive necrosis occurs in the infiltrated tissue, followed by the characteristic articular changes that are considered elsewhere.

In chronic cases uric-acid salts may be deposited in a great number of places in the body in the form of circumscribed masses, called *tophi*.

Calculi, or **stones**, are formed by the precipitation of solid substances from the fluids of the body. Calculi occur in the ducts of glands and in cavities lined with mucous membrane. The concretions found in blood-vessels, and due to calcification of thrombi, and in the tissue-spaces, such as the brain-sand already referred to, are, strictly speaking, also calculi. In the main all calculi consist of an organic or albuminous ground-substance, upon which a crystalline or granular material is precipitated. A great number of substances may act as the matrices or nuclei of calculi, such as desquamated cells, flakes of mucus, fibrinous masses, exudates, colloid substance, bacteria, and foreign bodies; around and in such bodies are then deposited crystalline or granular precipitates of varying chemical composition, depending upon the place of formation and the nature of the fluids in question.

Obstruction to and delay in the excretion of fluids, such as urine, bile, etc., accompanied by chemical changes in their composition, due to local or general causes, are the essential conditions which, in the presence of an organic matrix, lead to the formation of calculi.

The following are the more important calculi:

Biliary Calculi (Gall-stones).—Gall-stones are among the most frequent calculi. They occur oftenest after middle life, and after the sixteenth year they are found in 25 per cent. of all bodies. They are from two to four times as frequent in women as in men, a fact which is usually explained as due to a greater liability to biliary obstruction and catarrhal inflammation of the bile-passages in women on account of lacing and pregnancy, desquamated epithelium forming the necessary matrix for the deposition of precipitates from the bile. It has also been shown that bacteria (*B. coli*, *B. typhosus*, *staphylococcus*, and *streptococcus*) occur in the gall-bladder, where they may live for a remarkably long time. The occurrence of agglutination of the typhoid bacillus in the bile has been demonstrated, and various bacteria have been found in the center of gall-stones. Gall-stones have also been produced experimentally by injecting bacteria into the gall-bladder of animals.¹

Catarrhal cholangitis leads to epithelial desquamation and albuminous exudation; the bile becomes albuminous, and a compound of bilirubin and albumin is precipitated. Around this nucleus are then deposited various salts and other solid substances, their exact nature and ratio of admixture depending upon the composition of the bile. Naunyn has shown that cholesterolin and lime salts are largely produced by the mucous membrane of the gall-bladder, especially when the latter is the seat of catarrhal inflammation induced by bacteria (lithogenous catarrh).

According to their composition, biliary calculi are divided into cholesterolin, cholesterolin-pigment, biliary-pigment, and carbonate-of-calcium calculi. The most frequent are the first two, which have a crystalline fracture surface often showing lamination. The color varies according to the amount of pigment; pure cholesterolin calculi (rare) are practically colorless. The size and number vary greatly. When more than one calculus is present facets are usually formed on the stones, in consequence of mutual apposition.

The pigment calculi are usually small, irregular, crumbling masses, which often form in great numbers in cases of biliary obstruction.

¹ For references to literature, see Cushing, *Bull. Johns Hopkins Hosp.*, ix., 1898.

Urinary Calculi.—Obstruction to the urinary outflow favors the formation of stones, as it brings about changes in the stagnating urine that lead to the precipitation of various salts; it also induces alterations in the epithelium of the urinary tract, so that it may furnish the matrix for the formation of the stone; and it may further lead to infection of the urine, which in turn causes changes in the urine and the mucous-membrane.

General disturbances of metabolism also play a very important part, because they may lead to an overloading of the urine with substances that are easily precipitated, such as uric acid in gout, and that may cause necrosis of the epithelial lining. The albuminous organic matrix which is found in urinary calculi plays a decisive role in their formation; and it has been shown by Ebstein,¹ Naunyn, and others that such albuminous substances have the power to cause a precipitation of crystalline bodies from their solutions.

The composition of urinary calculi varies, depending on the one hand upon the composition of the urine as determined by the general metabolic processes in the body, and on the other hand upon changes in its composition, after its secretion by the kidney, due to bacterial and fermentative processes.

Urinary calculi usually manifest a gradual growth; the varying composition of the urine and the development of fermentation in the latter may serve to give the calculus a mixed composition; the conditions may be such as to lead to the formation in the same person of urinary calculi of different composition.

In the tubules of the kidney minute granules may form in poisoning with corrosive sublimate and other substances, the result of calcification of necrotic epithelial cells. In gout uric acid is frequently precipitated in the uriniferous tubules; while in the newborn the so-called uric-acid infarction (an unfortunate term) of the medullary pyramids of the kidney is often observed. It is due to the precipitation in the collecting tubules of uric-acid salts in the form of small yellowish masses, apparently embedded in an albuminous stroma, and giving the pyramids a yellowish or reddish striation. Uric-acid infarction occurs during the first two weeks of life, sometimes in fetal life, and is looked upon as being due to a metabolic disorder. Occasionally it gives rise to hemorrhage from the kidney.



FIG. 39.—Coral-shaped calculus in the pelvis of the kidney.

Urinary calculi may occur in the tubules of the kidney, the pelvis of the kidney, the ureter, the bladder, and the urethra. They present themselves as minute particles, known as sand or gravel, as rounded, smooth or rough, faceted stones of varying size and consistence; or as branching, coral-shaped casts of the pelvis and its calyces (Fig. 39). The following are the principal forms:

(a) *Uric-acid calculi*, composed of either uric acid or urates; (b) *phosphatic calculi*, composed of phosphate of calcium and phosphates of ammonium and magnesium; (c) *calcium-carbonate calculi*; (d) *calcium-oxalate calculi*; (e) *cystin calculi*; (f) *xanthin calculi*.

Fecal calculi are composed of layers of inspissated feces and lime salts.

¹ *Die Natur und Behandlung der Harnsteine*, 1884.

Salivary and *pancreatic calculi* are also composed of lime salts infiltrating an albuminous matrix produced by the epithelial lining of the ducts of the glands. The deposits often observed upon the teeth (tartar) are composed of lime salts, mucus, remnants of food, desquamated cells, and bacteria.

The consequences of calculi are discussed in connection with the morbid anatomy of the various organs in which they occur.

CYSTS.

Cysts are secondary consecutive formations that occur in different organs under similar conditions, and consequently merit a more general consideration.

In the broad sense, a cyst is a pathologic cavity provided with a distinct membrane enclosing fluid or semifluid contents. While the significance attached to the word cyst is not exact, yet the distinction between ordinary cysts and cystomas should always be kept in mind. A *cystoma* is a true tumor, arising from active proliferation of a matrix destined to form cystic spaces; whereas a cyst is a secondary formation not primarily due to tissue-proliferation. Cysts may be classified in the following etiologic groups:

Retention Cysts.—These cysts depend upon abnormal dilatation of glandular follicles and ducts, as well as other pre-existing cavities and canals, due to the accumulation of the secretion characteristic of the various structures in question. Retention cysts possess either an epithelial or an endothelial lining. The essential cause of retention cysts is obstruction to the outflow or failure of removal of the secretion that forms the contents of the cyst. The narrowing or closure of the duct of a gland or the outlet of a canal, through a contracting scar, external pressure, torsion of the duct, impaction of stones, foreign bodies, or thickened secretion, is followed by cystic dilatation if secretion still occurs behind the obstruction, and when the secreting parenchyma or membrane does not itself reabsorb the fluid. Such occurrences are frequent in the kidney. On account of the formation of fibrous tissue in its interior, in consequence of chronic interstitial changes, some of the uriniferous tubules become occluded from the pressure of the contracting fibrous tissue. The result is that the secretion dilates the canals and the capsules of the glomeruli into cysts of various sizes, the contents of which, at first clear and thin, may become greatly altered from obscure chemical changes as well as from degeneration in the lining of the cyst.

Further examples of retention cysts due to obstruction and failure of absorption are seen in the dilatations that form in the ducts and follicles of the sebaceous glands (comedo, milium, atheroma), in the mucous glands of the digestive and respiratory tracts, in the uterine glands (ovula Nabothii), in the canals of the epididymis, in the mammary gland, in the pancreatic duct, in the glands that open into the mouth (ranula), and also in larger canals, such as the ureters, the Fallopian tubes, the bile-passages, and the vermiform appendix.

In the case of closed glandular follicles an abnormally abundant or altered secretion or changes in the follicular walls may lead to cystic dilatation from failure of absorption. This variety of retention cysts is seen in the thyroid gland, the hypophysis, and the ovary.

In the instances of retention cysts above alluded to the lining of the cysts is epithelial, because the dilatations occur in structures normally lined

with epithelium. Retention cysts with endothelial lining may develop in lymph-vessels, in bursæ, and tendon-sheaths. Hydrocele, due to accumulation of serum in the tunica vaginalis testis, and cysts in the lymph-spaces of the neck and elsewhere, are examples of retention cysts with endothelial lining; bursæ and synovial sheaths also present cystic conditions the result of inflammation and irritation.

Cysts from Softening.—Cystic cavities with more or less distinct walls, but without either an epithelial or an endothelial lining, occur in a number of organs as the result of retrogressive changes, accompanied by disintegration and softening. Thus in the brain, hemorrhagic as well as anemic softening may be followed by the formation of cysts, due to encapsulation of the liquid or liquefied remainder of the clot or the softened area in a sac of connective tissue. And in many tumors, more especially sarcoma and carcinoma, extensive necrosis, fatty and mucoid degeneration, may give rise to cysts with fluid or semisolid contents.

Tubulo-cysts.—The cystic dilatations which frequently develop in functionless ducts and tubules, present in the body as remnants of embryonal structures, are called tubulo-cysts by Sutton. In these interesting cysts the process is essentially one of dilatation of a small pre-existing space by the gradual accumulation of fluid, produced either by secretion of the lining of the cavity or by transudation of the lymph-vessels and blood-vessels. Tubulo-cysts are therefore essentially retention cysts, differing from ordinary retention cysts in so far as they concern functionless remnants of embryonal structures that have undergone incomplete involution; from cystoma, in that the process of their formation is rather a mechanic dilatation than an active proliferation; and from some teratomas in the simplicity of their structure. In the last instance the difference is one of degree only.

The more detailed consideration of these cysts belongs elsewhere. Here it will suffice to enumerate the more important examples: parovarian, due to dilatation of the tubules of the parovarium or epoophoron (Wolffian tubules); vaginal, in connection with Gärtner's ducts; branchial, due to unobliterated remnants of the branchial clefts; cysts of the thyroglossal and omphalomesenteric or vitelline ducts.

Parasitic cysts, due to the presence in the body of parasites in a cystic or vesicular stage, such as echinococcus cysts (*Tænia echinococcus*), are of such a radically different origin from that of ordinary cysts that their consideration does not properly belong here.

The contents of cysts in general depend, first, upon the tissues in which they develop. Retention cysts may contain cholesterin, colloid material, serum, saliva, milk, sebaceous material, or mucus. Softening cysts may contain serous fluid, mucoid material, fatty detritus, and the remnants of tissue cells and blood-corpuscles. But the appearances and nature of the cystic contents vary and change much. Intracystic hemorrhages may occur; desquamated and degenerated cells and fragments from the lining membrane may become mixed with the fluid. The contents occasionally become inspissated, and then the remaining mass of detritus may undergo infiltration with calcareous particles.

The gradual dilatation of the tubular follicular structures and spaces in which cysts form is in some instances necessarily accompanied by new formation of tissue in the wall, and, in the case of cysts from softening, the wall is often formed by proliferation of the connective tissue, so that

while cysts cannot well be regarded as other than more or less retrogressive, secondary, or mechanic formations, the process need not be degenerative or passive in all its stages. It is also to be recollected that retention cysts often develop in connection with tumors in glandular structures, and it may be difficult or impossible to separate such cysts from the true cystic tumor, the *cystoma*.

The commoner secondary changes in the cyst-wall are inflammation, as a remote result of which the cavity may become obliterated, and calcification, the common fate of useless, dead, or dying tissue.

THE PROGRESSIVE CHANGES.

Introduction.—The progressive changes are observed in the regeneration of the various tissues after loss of substance by wear, traumatism, or necrosis, and in hypertrophy and hyperplasia. These changes are progressive not only because they are the result of increased cellular activity, but also because they serve to repair and to preserve structure and function, as shown so distinctly in regeneration. On the other hand, the cell proliferation that leads to the growth of tumors serves no such useful purpose.

The essential nature of progressive changes consists in the formation of new cells, and in some cases also in the enlargement of existing cells. The multiplication takes place according to the same laws that govern normal cell division. There is no pathologic type of cell multiplication; at the most, occasional modifications of the normal process may occur. It is therefore not necessary to detail here the phenomena of mitotic division, which is the essential form of multiplication, or of the amitotic, concerning the importance of which the opinions of cytologists still differ. Irregular mitosis, hypermitosis, and other changes in the nuclei in proliferation will be discussed in the section on Tumors.

An increase in the number of cells, called *hyperplasia*, takes place under a variety of circumstances. It occurs in most instances of hypertrophy; in all the forms of regeneration; in tumor growth; as the result of mechanic and chemical irritation; and from causes as yet unknown (leukemia, etc.).

In some cases the proliferation may be diffuse and uniform throughout the whole organ involved; in other cases it may be focal and circumscribed, or it may affect one variety of cells to the exclusion of others. This occurs, for example, in chronic inflammations, in which there may be more or less isolated hyperplasia of the connective tissue.

As will be shown in the study of regeneration of tissues, the different kinds of cells in the body possess an unequal degree of proliferative power. Generally speaking, the younger the individual the greater the faculty of multiplication of the cells. Cells that are highly specialized, as ganglion-cells, bone-corpuscles, and striped-muscle cells, have but little power of proliferation; but surface epithelium, glandular cells, and connective-tissue cells possess marked regenerative powers.

The division of pre-existing cells gives rise to embryonal or formative cells, which by further changes and by the secretion of an intercellular substance form the definitive tissue; the subsequent development follows the same general rules in pathologic as it does in physiologic proliferation.

It is almost universally recognized that a cell gives rise to another cell of the same kind only; *e. g.*, an epithelial cell forms a new epithelial cell, and

not a connective-tissue cell, and a connective-tissue cell a connective-tissue cell. This is the law of the specificity of cells. *Omnis cellula e cellula ejusdem generis*. It is true that the connective tissues—cartilage, bone, myxomatous tissue, and ordinary connective tissue—are able each one to form all the other members of the group; but it is to be remembered that the active proliferation occurs, in each instance, in mesoblastic connective-tissue cells, the difference in the structure of the mature tissues being due to the different intercellular substances produced in each instance. According to Hanseemann,¹ this law of specificity, which at the present time is quite generally recognized, at least in the higher animals, is also demonstrated by appreciable differences in the mitoses of the various tissues, the form, size, and number of chromosomes being characteristic for the cells of each particular tissue.

While the real cause of cell division and cell multiplication is not known, yet the essential conditions necessary for cell proliferation have been determined to a considerable extent. Many cells seem to have a constant tendency to proliferation; this is demonstrated, for instance, by the facts learned from transplantation. Transplantation is the bringing of pieces of one tissue into or upon another and securing their growth. It is made possible by the fact that certain cells retain their power of proliferation after they have been removed from their original place of development and growth. Thus, periosteum, bone-marrow, and cartilage have all been transplanted successfully into soft parts and into blood-vessels (Cohnheim and Maas).² It has been found that it is especially young tissue that will grow, and that growth after a time comes to a standstill and may be succeeded by atrophy. This atrophy in the case of transplantation with osteogenetic tissue undoubtedly depends upon disturbances or absence of function. Transplantation of skin was shown by the researches of Reverdin and Thiersch to be so uniformly successful that it has come to be extensively employed in practical surgery for the purpose of covering large open wounds. Small flat pieces of skin are removed with the scissors or razor so as to include the epidermis, the rete Malpighii, and the upper layers of the corium, and then placed on the granulating surface and protected by suitable dressings.

The strips of skin are at first held fast by the coagulation of fibrin and nourished by transuded fluid; but soon embryonal vessels reach the transplanted part, and while the epidermal layers desquamate the deeper layers soon begin to form new epithelial cells and become the centers for a progressive new formation of permanent epithelium, which is provided with a horny layer by the metamorphosis of the cells upon the surface. Duhamel and John Hunter³ succeeded in transplanting spurs and teeth into the cock's comb, and Paul Bert made a rat's tail grow fast under the skin of its back.

From these and other experiments and observations it has been learned that young cells possess a greater power of proliferation than the old; that the transplanted cells must be abundantly nourished from the circulating blood; that the new-formed tissue soon undergoes atrophy if deprived of the stimulus of function; and that transplantation of tissue is successful only in animals of the same species.

Many animal cells remain alive for days after the general death of the organism. This power of independent existence has been called by Virchow

¹ *Die Specificität, Altruismus, und Anaplasie der Zellen*, 1893.

² *Virchow's Archiv*, lxx., 1877. ³ *The Natural History of the Human Teeth*, 1803.

the *vita propria* of cells. Periosteal cells have been found to retain their osteoplastic faculty for as long as one hundred and ninety-two hours after removal from the body (Morpurgo); and human cutaneous epithelium proliferated and produced living epithelial covering, when grafted on wounds, after having been kept outside of the body aseptically for from ten to twenty or more days (Ljunggren, Wentscher¹).

By some the tendency of cells to proliferate is regarded as connected with the nucleus. Under normal conditions the tendency is held in check, the stimulus to proliferate and the strength of the restraining influences being equally balanced. This equilibrium may be disturbed under pathologic conditions; on the one hand by factors that diminish or remove the restraining influences, and on the other hand by factors that stimulate the formative irritability of the cells, as Virchow states it. It is probable that the restraining influences are in part mechanic, due to the mutual pressure exerted by the cells composing a tissue, in part due to chemical conditions connected with the nutrition of the cells. These restraining influences become so relaxed and modified whenever destruction of cells occurs from any cause that the processes leading to cell division at once begin, and new cells are formed until equilibrium is again restored—*i. e.*, until as perfect regeneration as possible has been accomplished. That perfect regeneration often fails to take place depends upon such factors as insufficient power of proliferation, due to the age of the cells, their highly specialized state, insufficient or unsuitable nourishment, and upon the relatively greater regenerative faculty of less highly differentiated cells, as connective-tissue cells, the consequence being that very frequently the loss of substance is replaced largely by connective or scar tissue. At all events, regeneration may be ascribed, theoretically, as largely due to the removal or suspension by the wound or the cellular necrosis of the influences that in the structurally perfect tissue hold the tendency of the cells to multiply under control. That other factors than injury may lessen the restraining influences referred to cannot be denied, because cell proliferation also occurs under a number of conditions not associated with demonstrable trauma and necrosis.

The frequent occurrence of cell proliferation in tissues the seat of long-continued passive hyperemia has been ascribed to the increase of the nutritive supply, on the assumption that the nutrition of the cells is more of a passive process; but this view does not commend itself, because the nutrition of the cells is one of the manifestations of cellular activity, necessarily dependent, however, upon the presence of suitable food. It does not follow that an overnourished cell possesses an increased formative tendency. It is doubtful whether the infrequently renewed venous blood of passive congestion contains the elements capable of producing overnutrition. It is most probable that the proliferation in passive congestion is regenerative in character, and induced by the destruction of some of the more highly developed cells of the congested tissue.

It has been shown that a moderate degree of heat increases metabolism, and that the growth of the tissues in young animals is stimulated by a temperature of from 37° to 40° C.; whereas a temperature of from 10° to 12° C. delays growth and cell multiplication (Penzo).

There also seems to be no doubt that increased functional activity stimulates the nutritive as well as the formative action of the cells. The hyper-

¹ Ziegler's *Beiträge*, xxiv., 1899.

trophy and hyperplasia of increased labor (page 133) is best explained as due to a stimulation of the formative activity of the cell on account of the unusual demands made upon its functional capacity; that nutritive influences also play an important and sometimes decisive part in proliferation is shown, for instance, by the absence of hypertrophy of the heart under conditions that otherwise usually lead to its development, when there is a general malnutrition, as in chronic pulmonary tuberculosis or carcinoma of the stomach.

Whether traumatic, toxic, and infectious influences are capable of directly stimulating the cells to proliferation is a question that can hardly be answered definitely at the present time. In the majority of instances these agents produce either necrosis or necrobiosis of the cells with which they come in contact, and the proliferation that follows must be looked upon as regenerative in its nature, intended to fill the defect that has resulted. Often the proliferation extends beyond the requirements of regeneration. This question is of great importance in connection with the tissue proliferation that occurs in many chronic inflammations. The results of certain experiments seem to make it probable that chemical and bacterial agents may be able to incite cell proliferation directly. According to Baumgarten,¹ the first effect of the tubercle bacilli upon the rabbit's cornea is to excite cell division; Wegner² states that the administration of phosphorus directly increases the growth of bone; and Ziegler and Obolonsky³ found that small doses of arsenic and phosphorus seem directly to stimulate the cells of the liver and kidney to proliferation.

From these considerations⁴ concerning cell proliferation under pathologic conditions it may be concluded:

1. That the proliferation follows the physiologic types of cell division.
2. That the law of cell specificity is generally obeyed.
3. That proliferation is most active in young, well-nourished, only slightly differentiated cells.
4. That proliferation occurs under conditions that remove the restraint normally checking cell division, such as traumatism and necrosis; or that stimulate the formative activity of cells, such as increased function, heat, and certain chemical substances; or that operate in both ways at the same time.

REGENERATION.

Regeneration is the process by means of which portions of tissue lost are replaced by new tissue of the same, or approximately the same, structure as the original. It begins, as already indicated, with the formation of new cells by division of the pre-existing cells. These new cells are formative embryonal cells, which by further modifications and the secretion of an intercellular substance form the definitive permanent tissue.

Regeneration may take place not only after solutions of continuity due to external or violent means, such as wounds, but also after the destruction of cells such as occurs in the various forms of necrosis and degeneration that have been described. It depends, as stated above, upon certain peculiar qualities in the animal and human tissues that are not as yet understood,

¹ *Ueber Tuberkel u. ueber Tuberkulose*, 1885.

² *Virchow's Archiv*, lv., 1872.

³ *Ziegler's Beiträge*, iii., 1888.

⁴ An able discussion of some of the problems referred to is found in an address by Welch, on "Adaptation in Pathologic Processes," *Trans. Am. Phys. and Surg.*, iv., 1897.

but which are connected with changes in the environment or nutrition of the cells in the vicinity of a defect, in consequence of which the influences that hold in check the inherent tendencies of many cells to proliferate are overcome.

The power of regeneration in human tissues is limited as compared with that of many of the lower animals, in which whole organs and extremities may be produced. As a general rule, the higher the tissue stands in the scale of differentiation the smaller the tendency of its cells to proliferate. Thus, ganglion-cells are not reproduced to any extent, if at all, in the adult (the axis-cylinder, however, is easily regenerated), and many glandular epithelial cells have a relatively limited reproductive power; whereas the surface epithelium, the epithelial cells in the lining of ducts, and particularly the connective-tissue cells, have great power of regeneration. This unequal degree of regenerative faculty of the various histologic elements composing an organ or tissue is one of the factors that may lead to imperfect regeneration. In case the defect is not repaired by tissue of the same structure as the original, then substitution with connective tissue takes place. It is characteristic of connective tissue to fill all spaces not occupied by other cells, and this is also observed in the regeneration of pathologic defects. This imperfect, partial regeneration is designated as scar-formation.

The further study of regeneration necessitates a description of the regenerative processes as they present themselves in the individual tissues.

The Formation of New Blood-vessels.—New blood-vessels are formed whenever any considerable degree of hyperplasia or regeneration takes place. They are of the greatest importance, and, indeed, are often absolutely necessary in order that the proliferating tissue may receive sufficient nutrition. The formation of new vessels is therefore one of the very first as well as one of the most essential steps in nearly all forms of tissue proliferation.

Three kinds of vascular new formation have been described, namely, the primary, the secondary, and the tertiary.

The primary is the one observed in the embryo. The original view was that the cells of the mesoblast became hollow, the central part giving rise to red blood-corpuscles, while the remaining shells coalesced with each other to form the lumen and the wall of capillaries (Billroth).¹

In the secondary form spindle-shaped cells were believed to arrange themselves in rows so that an intercellular canal was formed, the lumen of which subsequently came into communication with the lumen of pre-existing capillaries.

The tertiary form was characterized by the development of budding processes in the walls of old capillaries, which united with similar processes, became hollow, and formed new capillary vessels (Billroth, Arnold²).

The secondary form is well demonstrated, although it is possible that in some newly formed tissues a certain degree of provisional circulation may make its way through intercellular canals and spaces without distinct walls. Regarding in the primary form Thoma³ and others claim that the development of the capillaries is not, as usually described, an intracellular, but an intercellular process, the mesoblastic cells arranging themselves in rows, the polygonal cells surrounding these spaces gradually changing into flat endo-

¹ *Die Entwicklung der Blutgefäße*, 1856. ² *Virchow's Archiv*, liii. and liv., 1871.

³ *Histogenese u. Histomechanik des Gefäßsystems*, 1893.

thelial cells. The primary form is not observed in the postembryonal period. The formation of vessels by budding (tertiary form) occurs in the embryo after the first network of capillaries is formed, and this is probably the only form of production of new vessels in postembryonal life.

The formation of new vessels by budding or sprouting presents in the main the following details: The protoplasm of an endothelial cell in a capillary wall becomes large and swollen, and sends out a solid, more or less wedge-shaped process or sprout, which ends in a long, fine, free thread.

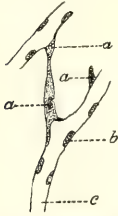


FIG. 40.—Formation of new capillaries by budding: *a*, budding process; *b*, nucleus of endothelial cell; *c*, capillary.

At about the same time the endothelial cells multiply by mitosis, and nuclei are seen in the protoplasmic bud. Subsequently the thread-like end unites with a similar prolongation from a neighboring sprout, or with the wall of either an adjacent capillary or of the capillary from which it sprang. Then this solid protoplasmic bridge becomes hollow; usually this occurs first at its point of origin, and blood at once enters the sprout, which gradually dilates and becomes pervious throughout to the point of entrance into another capillary; in this way a new passage for the blood is formed. The canalization sometimes begins from both ends of the protoplasmic bridge at the same time. New buds may spring from the original protoplasmic sprouts, quite a network of capillaries arising in a

very short time (Figs. 40 and 41).

The protoplasmic process from the endothelial cell must be regarded as a new cell after it has received its nucleus; and the formation of the new vessel is primarily an intracellular process, brought about by central canali-



FIG. 41.—New capillaries in a blood-clot on the inner surface of the dura mater. $\times 600$.

zation of the cells. As more nuclei develop in the homogeneous wall of the new vessel, new cells gradually appear, which are arranged so as to form a hollow cellular tube, in which the borders of the flat endothelial cells can be demonstrated by means of injections of silver-nitrate solution (Arnold). According to Ziegler, spindle-shaped or branching formative cells may unite

with the processes from the cells of the vessel-wall, become canalized, and thus aid in the forming of new capillaries.

The new capillary wall soon becomes thickened, either from proliferation of the endothelial cells or by the apposition of new formative cells from the surrounding tissue.

Every new formation of vessels begins with the production of capillaries. If new arteries and veins are formed, which always occurs in extensive tissue proliferation, then the lumen of the new capillaries undergoes dilatation and the wall increases in thickness. Whether this increase in thickness is due entirely to multiplication of the cells in the wall of the capillary or to apposition from without is not altogether clear; the method of new production of the muscular and elastic elements peculiar to arteries and veins is also not well understood.

Regeneration of Blood-corpuscles.—The regeneration of leukocytes takes place in the lymph-glands and lymph-follicles, the spleen, and the lymphoid bone-marrow. It has also been shown that the leukocytes may multiply in the circulating blood and in the tissue-spaces. The multiplication occurs both by mitotic and by amitotic division. The mitotic division gives rise to more durable and more vigorous cells than the amitotic division (nuclear fragmentation).

The regeneration of the red blood-corpuscles has been extensively studied, but unanimity of opinion concerning many details has not yet been reached. The studies of Neumann, Bizzozero, and others have established the presence of nucleated red blood-corpuscles—hematoblasts—in the bone-marrow of adults, and also that these cells divide by way of mitosis. It is generally agreed that in health regeneration of red blood-corpuscles occurs in the vessels of the bone-marrow, in which are found numerous nucleated red cells with karyokinetic figures. Inasmuch as the peripheral blood does not, as a rule, contain any nucleated red blood-corpuscles, it must be taken for granted that the regeneration occurs entirely in the bone-marrow, and that only the non-nucleated cells reach the general blood-stream. The transformation of nucleated into non-nucleated cells is due, according to most authors, to the vanishing (solution or extrusion) of the nucleus (Howell).¹

When generation of red blood-corpuscles goes on very actively, as, for instance, after an extensive hemorrhage or in chronic anemia, nucleated red cells may pass out from the marrow into the circulating blood.

It is in regard to the origin of the nucleated red cells of the bone-marrow that the opinions of investigators differ most. Bizzozero and Flemming hold that the nucleated red cells of the bone-marrow are direct descendants of the nucleated red cells of the blood of the embryo; these cells are collected in the blood-vessels of the marrow, and produce by mitotic division a continuous series of generations of nucleated cells, which change into the non-nucleated as occasion requires. Howell, Denys, and others believe, on the contrary, in the existence of colorless erythroblasts which change in the bone-marrow to hemoglobin-containing nucleated cells that afterward lose their nuclei and become the ordinary red corpuscles. These erythroblasts are formed, according to Löwit, in the bone-marrow and the lymph-glands.

Neumann finds Flemming and Bizzozero's conclusions inadequate. They do not explain the postembryonal formation of bone-marrow containing nucle-

¹ *Jour. of Morphology*, iv., 1890.

ated red corpuscles, as occurs when fatty marrow becomes lymphoid and when entirely new marrow is formed. He assumes, therefore, that nucleated red cells may develop from leukocytes or from the cells of the marrow.

Regeneration of Epithelium.—The view that connective-tissue cells play some part in epithelial hyperplasia and regeneration has been abandoned. The investigations of recent years have shown that epithelial cells originate only from epithelial cells; that the regeneration of epithelium occurs only from the multiplication of pre-existing epithelial cells; and, furthermore, that pathologic new growths of epithelial cells always spring from epithelium.

In all these instances the formation of new epithelial cells takes place by karyokinesis. Occasionally the body of an epithelial cell sends out processes which receive nuclei, separate from the maternal cell, and become independent cells.

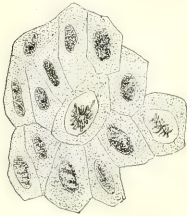


FIG. 42.—Mitotic figures in regenerating corneal epithelium in a rabbit forty-eight hours after scratch with the point of a knife. Corrosive sublimate; paraffin; hematoxylin. $\times 1000$.

The epithelium covering the cutaneous and mucous surfaces is constantly undergoing desquamation, even under physiologic conditions, and the desquamated cells are replaced by mitotic multiplication of the remaining cells.

The regeneration of surface epithelium after loss of substance due either to traumatism or to necrosis and ulceration is usually perfect. In the intestine the surface epithelium, when lost, is replaced by proliferation of the cells in the follicles of Lieberkühn. The appendages of the skin, such as the hair and nails, are also reproduced, if parts of the hair-follicle and of the nail-matrix remain undestroyed. The epithelium of the cornea, which has been used extensively for the purpose of studying the histologic processes of regeneration, reproduces itself rapidly (Fig. 42).

It is possible that the epithelium of the sweat-glands and sebaceous glands may take part in the regeneration of the surface epithelium of the skin. Isolated islands of epithelial cells appearing in the center of granulating cutaneous surfaces, such as every surgeon has observed, spring in part at least from sweat-glands or sebaceous glands. In wounds of the trachea and the stomach it has also been shown that the epithelial cells of the gland-ducts take part in furnishing a new surface epithelium.

According to Fürst,¹ moderate degrees of heat and cold increase the capacity of the epithelial cells for regeneration.

Glandular epithelium is also capable of rapid regeneration. Thus, the liver possesses an extraordinary reproductive power; Ponfick² and Podwyszołski³ have found that the experimental removal of more than one-half of the organ is sooner or later fully replaced. Podwyszołski has also shown that after wounds of the liver cell-division by karyokinesis begins on the second day. In wounds and necrosis of the liver karyokinetic figures occur freely in the epithelial lining of the bile capillaries, as well as in the surrounding hepatic cells. The exact parts played by the epithelium of the biliary ducts and by the liver-cells proper in regeneration of the liver have not been accurately determined. In extensive wounds of the liver, as well

¹ Ziegler's *Beiträge*, xxiv., 1899.

² Virchow's *Archiv*, cxviii., 1889.

³ Ziegler's *Beiträge*, i., 1886.

as of other glands, the defect is closed by connective tissue, into which grow new-formed glandular structures to a greater or less extent.

The thyroid gland has been shown by Ribbert¹ to be capable of considerable local regeneration, even when it is the seat of goiter. The epithelium of the old follicles multiplies rapidly, and produces columns of cells that may arrange themselves so as to form new follicles.

The epithelium of the kidney is also capable of proliferation, and small losses in the tubular epithelium are rapidly replaced; but in wounds there is no restoration of the continuity of the tubules (Penzo, Barth). Extirpation of one kidney is followed by an adaptive or compensatory hypertrophy of the remaining organ, the beginning of which is indicated by the appearance of karyokinetic figures in the epithelium of the uriniferous tubules as early as the third day. Martinotti² has shown that while the old cells of the kidney excrete indigo-sulphate of sodium when injected into the blood, the new cells with karyokinetic figures do not take part in this process.

Cornil and Carnot have shown that the epithelium of the mucosa of the urinary bladder and the gall-bladder in the dog possesses a marked power of regeneration, especially that of the urinary bladder.

Ulcerative processes involving the mucosa and submucosa of the stomach and intestine, as well as defects produced by wounds, are followed by regenerative changes, in which new glands may be formed. The regeneration of the glands commences in the epithelium of the old glands, which proliferates and sends out new processes and tubules that spread over the base of the defect, filling the depressions and recesses. In this way even extensive ulcers may become clothed with a glandular mucous membrane; usually the arrangement of the glands in such cases is more or less atypical. In some cases the proliferation of the glandular tubules becomes excessive, and extends beyond the normal limits of the mucous membrane. This has been observed in the margin of healing gastric ulcers, and has been regarded as showing that the absence or diminution of the normal resistance to proliferation may act as a stimulus to the latter, and thus give rise to the growth of tumors (Ribbert).

As a general rule the various forms of epithelial cells are not interchangeable; flat epithelium produces flat, cylindric epithelium produces cylindric, etc. To this statement there are exceptions. In long-continued inflammations of various mucous membranes, accompanied by repeated desquamation of the epithelial lining, the continuously regenerating epithelium may change its form, so that a mucous surface covered with ciliated columnar epithelium becomes clothed with squamous cells. This has been observed to occur in the nose in *ozena* (Schuchardt); in the gall-bladder; in the uterus in the case of inversion, in uterine polypi projecting into the vagina, and in chronic endometritis (*ichthyosis uteri*, Ries³); in the middle ear in the case of polypoid formations that have penetrated the tympanic membrane and have reached the external canal. Under these circumstances superficial epidermization with flat cells may take place. In papilloma of the urinary bladder the stratified epithelium is replaced by cylindric cells.

The change of one form of epithelial cell into another is called epithelial metaplasia.

Regeneration in the Nervous System.—While peripheral nerves

¹ *Virchow's Archiv*, cxvii., 1889.

² *Centralb. f. allg. Path. u. path. Anat.*, iii., 1892.

³ *Ann. Gynec. and Obstet. Jour.*, 1896.

are capable of complete regeneration, the central nervous system of man has no marked regenerative power. In animals the conditions vary; in many lower species and in newborn dogs and rabbits (Eichhorst and Naunyn¹) partial or complete regeneration has been observed after experimental injuries. In man wounds may be succeeded by the appearance of mitosis in adjacent ganglion-cells, but these do not appear to multiply (Sanarelli); after focal lesions, such as embolic and hemorrhagic softening, the defect is usually not filled in, even with scar-tissue, but a cavity is formed, the walls of which may show a zone of proliferating glia-tissue and a thickening of the perivascular connective tissue, but there is no regeneration of the nervous elements proper. Stroebe² has shown that in experimental wounds of the spinal cord the cut axis-cylinders, especially those of the pyramidal tracts, may grow out again to a certain degree, but not sufficiently to result in complete restoration, the defect being filled, as in man after similar injuries, with glia-tissue.

Regeneration of peripheral nerves presents many exceedingly interesting manifestations. It is in reality the regeneration of a part of a cell, inasmuch as the essential element concerned is the neuraxone, or axis-cylinder, which is part of the neurone.

Regeneration of the peripheral nerves has been extensively studied; while the interpretations of the microscopic appearances by the older authors differ greatly, recent investigators, such as Ranvier, Vanlair, Stroebe, Huber,³ and others, aided by an improved technic, have arrived at more uniform conclusions, although agreement has not yet been reached regarding all points.

When a peripheral nerve is cut, complete degeneration of the neuraxones and of the medullary sheaths distal to the wound follows, because those parts of the nerve have been severed from the centers of the neurones—the neurocytes. Central to the wound similar degeneration occurs in the cut ends up to the first or second Ranvier's node. This degeneration is characterized by disintegration of the medullary sheaths into drops and particles, while the neuraxones change into small fragments that soon disappear. Subsequently this detritus is gradually removed (Fig. 43). During this degeneration the nuclei of the sheaths of Schwann undergo mitotic division, and form protoplasmic cells which may coalesce into bands.

The division of a neuraxone is succeeded by certain obscure changes, such as chromatolysis, etc., in the corresponding neurocyte or ganglion-cell, which by some are interpreted as of a progressive and regenerative nature.

The regeneration of the nerve begins in the end of the central stump: the neuraxones swell up at the ends and split into from two to five new axones, which grow in a peripheral direction. Under the usual circumstances

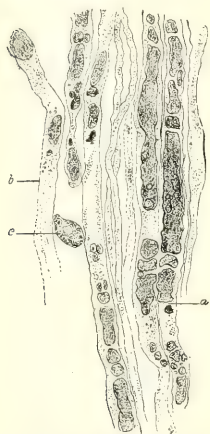


FIG. 43.—Degeneration in the sciatic nerve of a rabbit ten days after experimental division: *a*, neurilemma containing drops and fragments of myelin; *b*, empty neurilemma; *c*, leukocyte filled with detritus. Flemming's solution; paraffin; safranin. $\times 250$.

¹ *Arch. f. exper. Path.*, ii., 1874.

² *Ziegler's Beiträge*, xv., 1894.

³ *Jour. of Morphology*, xi. (with references).

the majority enter the peripheral part of the cut nerve and advance in its endoneurium and perineurium, or in the old neurilemma-sheaths (Fig. 44), until, after weeks or months, complete regeneration and functional restoration take place. Many axones may pass by the end of the peripheral stump and extend into the adjacent tissue. Perfect apposition of the cut ends and the interposition of as little as possible of the granulation-tissue which always forms in the wound favor the growth of the new neuraxones within the old nerve; a dense cicatrix between the ends may prevent the down-growth of the fibers. According to Vanlair, regenerating nerves may grow from 0.2 mm. to 1 mm. a day, according as the tissue they penetrate is favorable or not. In the completely regenerated nerve the rearrangement of the new fibers into bundles takes place a certain distance below the wound.

The new axones gradually receive medullary sheaths, which at first have a varicose appearance; the origin of the myelin has been traced to the cells

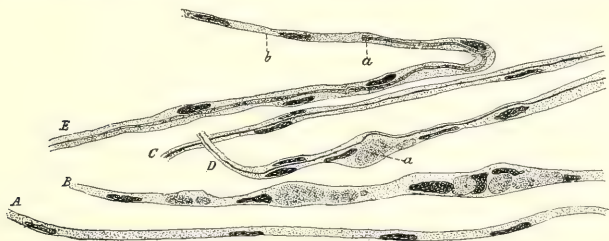


FIG. 44.—Teased specimen of divided nerve one hundred and seventeen days after section (after Huber). *A*, completely degenerated fiber; no regeneration. *B*, degenerated fiber containing balls of broken-up myelin. *C* and *D*, new fibers with axis-cylinders and nerve-corpuscles; at *a*, fragment of myelin. *E*, fiber with axis-cylinder ending in slight enlargement at *a*; *b*, continuation of old sheath containing protoplasm and nerve-corpuscles. Stroebe's stain. $\times 700$.

of the sheath of Schwann, but it is more likely that the new myelin covering is the result of a continuous down-growth of the old.¹ In fact, the claims that the new axones and myelin sheaths result from the union of pieces produced by the cells of Schwann's sheath are not in harmony with our present conception of the neurones. The cells of Schwann's sheath are connective-tissue cells, and their function in regeneration of nerves seems to be phagocytic, rather than the formation of parts of the neurones proper.

Huber has shown that after loss of substance in peripheral nerves regeneration and restoration of function are materially favored by implanting between the resected nerves a loose segment of a nerve. The implanted segment and the peripheral stump, together with about 0.75 cm. of the central stump, degenerate, and both the implanted segment and the degenerated nerves soon present the same structure, namely, collapsed sheaths containing nucleated protoplasmic bands; the new axones grow into and between the sheaths of Schwann. The implanted piece of nerve serves as a path along which the new axis-cylinders can grow into the old nerve. Various other substances, such as catgut, bone tubes, etc., have been used for the same purpose, but not with such satisfactory results.

When the central end of a completely severed nerve is placed outside of

¹ Kölster, *Ziegler's Beiträge*, xxvi., 1899.

communication with the peripheral part, as occurs in amputations and very extensive wounds, a mass of embryonal connective tissue forms around the end of the nerve. Axones may sprout from the end of the nerve-stump and grow into the cicatricial tissue in all directions, forming a distinct bulbous enlargement of the nerve-end. This is the so-called amputation neuroma. It represents an effort at regeneration of the axones.

Regeneration of Muscular Tissue.—Striated muscular tissue is capable of a certain degree of regeneration. New muscular tissue is formed only from the old, and not from connective tissue, which may, however, take part in the formation of the sarcolemma of the new fibers. The regeneration of striated muscular tissue can take place independently of any nerve-supply. It has been studied as it occurs after experimental wounds and after necrosis in typhoid fever (Waldeyer, Neumann, Nauwerck, Volkmann,¹ and others).

Regeneration of muscular tissue begins with the mitotic division of the nuclei of the contents of the sarcolemma. The new nuclei lie upon as well as in the spaces between the split ends of muscular fibers. There is soon noticed the formation of new protoplasm around the nuclei, and large multinucleated protoplasmic masses form, into which the existing striated muscular substance passes without sharp limits. The new muscular fibers develop from these multinucleated protoplasmic masses, increasing in size and length, and gradually presenting first a longitudinal and then a transverse striation. The new muscular fibers frequently split up into two or three narrower fibers, so that more fibers result than originally were present.

The dividing muscle-cells that are not in connection with living sarco-plasm also change into multinucleated protoplasmic masses, which often contain hyaline substance and fragments of old fibers. Such masses are usually found in great numbers in the early scar after wounds or necrosis of muscle. While the larger part of these cells probably disintegrate, it is likely that some of them change into striated muscle-substance, and form either new muscle-fibers or become united with old muscle-fibers or with new buds. This is the regeneration in discontinuity of Volkmann, and occurs especially after necrosis of muscle in typhoid fever.

Reproduction of the muscular tissue of the heart occurs to an extremely limited degree. Wounds and necroses heal by means of scar-tissue.² Hypertrophy of the heart is chiefly a true hypertrophy, although it is probable that some hyperplasia takes place.

The reproduction of smooth muscle-fibers occurs to a certain extent after traumatic and other necroses, as well as in hypertrophy and in tumors. The regeneration occurs by mitotic cell division. Whether transformation of embryonal connective-tissue cells into smooth muscle-fibers occurs, as was thought by Kölliker, and whether there is ever metaplasia of smooth muscle-fibers into striated, as maintained by Busse, is still undecided. The power of regeneration of smooth muscle seems to be limited, as wounds in the muscular coat of the stomach, the intestine, and the urinary bladder are largely closed by scar-tissue.

Regeneration and Metaplasia of the Connective Tissues.—The connective tissues—ordinary connective or fibrous tissue, periosteum, bone, cartilage, myxomatous and fatty tissue—are all made up of embryologically equivalent mesoblastic cells, the marked variations in the structure

¹ Ziegler's *Beiträge*, xii., 1893 (with references).

² Elsberg, *Jour. Exper. Med.*, iv., 479, 1899.

of the mature tissues depending essentially upon the differences in the intercellular substance.

The regeneration of these tissues begins with the production of an indifferent embryonal or formative tissue, from which the definitive tissue is produced by the development of peculiar intercellular substance. The connective tissues are also able to change the one to the other without the intervention of an embryonal stage by a change of the intercellular substances only, a process called metaplasia. Thus, cartilage may change into bone, and fibrous connective tissue into cartilage, etc., by a transformation of the matrix in each case.

The mature connective tissues possess different degrees of regenerative power. It is most marked in the ordinary fibrous connective tissue, in periosteum, and in the medullary tissue of bone; whereas cartilage and bone-substance proper possess but little ability to form new tissue, so that in them larger defects are repaired either by proliferation of periosteum (perichondrium) or of ordinary connective tissue with subsequent differentiation of the matrix, or the defects are filled with scar-tissue.

The question of the development of connective tissue from hematogenous cells is touched upon in the discussion of inflammatory granulation-tissue. The theory of Shakespeare, and more particularly of Grawitz, that the intercellular substances of many tissues, as the tendon, for instance, contain invisible slumbering cells that are roused into active proliferation by the influence of regenerative and other stimuli, is not supported by any facts that would warrant its discussion at the present time.

Regeneration of connective tissue begins with mitotic division of pre-existing cells. If defects of any extent are to be repaired, the proliferation continues actively until a mass of young cells is produced—embryonal, formative, or granulation-tissue. Simultaneously new capillaries are formed by budding processes from the old. It is quite likely that the capillary endothelial cells also give rise to formative cells, as already described. The embryonal cells are larger than the small mature cells of the connective tissues; the form of the cells varies, depending upon conditions of pressure and upon the age of the cells; round, oval, spindle-shaped, and branching cells are observed; the nuclei are large, often vesicular, and there may be large cells with two or many nuclei—giant cells. These formative cells have received various names, depending upon the kind of mature tissue they are destined to form in the process of further differentiation—if fibrous tissue, fibroblasts; if cartilage, chondroblasts; and if bone, osteoblasts.

Fibrous Tissue.—When fibrous tissue is reproduced, as in the healing of wounds and defects in the organs and tissues of the body, there is formed an intercellular substance, or matrix, in part homogeneous, in part fibrillated. Concerning the manner of formation of the intercellular substance, investigators express different opinions. Some claim that the fibroblasts produce a homogeneous intercellular substance which subsequently becomes more or less finely fibrillated; others, that the protoplasm of the cells first forms fibrillæ in its peripheral layers, which are subsequently deposited between the cells; the direction in which these fibrillæ run is determined by the mechanic tension of the tissue.

The manner in which new elastic tissue is formed is not definitely known. The new formation of elastic elements has been studied lately, especially in various forms of endarteritis. Some investigators hold that they are formed

by chemical changes in the stroma, others by such changes in the protoplasm of connective-tissue cells.¹ As the intercellular substance is formed the fibroblasts become smaller and flattened, and lie as fibrous connective-tissue corpuscles in small spaces in the matrix. When a wound or defect becomes filled up with a finely fibrillated connective tissue produced in this manner, a scar or cicatrix is said to have formed.

Cartilage.—Formative tissue composed of chondroblasts may be produced to a limited extent by existing cartilage-cells, but originates generally from mitotic division of cells in the periosteum or perichondrium, the medulla of bone, and sometimes in connective tissue. The chondroblasts produce a hyaline intercellular substance which gradually increases in amount, while the cells become smaller and lie as cartilage-cells in small round cavities, about which the matrix becomes more dense, so as to form a sort of capsule for the cells (Fig. 45). New cartilage is also frequently produced by metaplasia. This occurs, for example, in the perichondrium of growing cartilage by a gradual change of its fibrillated intercellular substance into the homogeneous hyaline material of cartilage, while the connective-tissue cells assume the form of cartilage-cells. Hyaline cartilage may change into fibrocartilage by the formation of fibrillæ in the matrix. Cartilage may by metaplasia change into the other connective tissues.

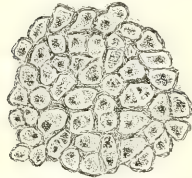


FIG. 45.—New-formed cartilage about a seven-day-old fracture of the tibia in a rabbit. Flemming's fixation; saf-ranin. $\times 450$.

Bone.—The formative tissue arises principally from the cells of the periosteum, the perichondrium, and the bone-marrow; but it may be produced by fibrous connective tissue. The osteoblasts become separated by a homogeneous or densely fibrillated ground substance, which subsequently becomes impregnated with lime salts; while the osteoblasts change into small irregular cells, which come to lie in small cavities as the bone-cells of mature bone. Before calcification takes place the ground substance is known as osteoid tissue. The formative tissue between the areas of osteoid tissue changes into the structure of bone-marrow; the cells send out processes which unite with those from other cells at the same time as a sparsely fibrillated, fluid, intercellular substance is formed, and in this substance the cells characteristic of bone-marrow are subsequently deposited. When the osteoid tissue has become infiltrated with lime salts the osseous structure is completed.

Usually, however, this process of bone formation is associated with metaplastic changes. Thus, the formative tissue may first produce hyaline cartilage, which subsequently becomes vascularized, and then by metaplasia changes into osteoid tissue, which becomes impregnated with lime salts, while the cartilage-cells become bone-cells. Osteoid tissue is distinguished from osseous tissue by the absence of lime salts, and from cartilage by the irregular outline of the cells and the greater density of the intercellular substance. These various processes are described more completely in connection with the healing of fractures. Connective tissue as well as pre-existing cartilage may also change into bone directly, according to the principles of metaplasia.

Fat Tissue.—New fat tissue may arise by the deposition of fat in the

¹ Jores, "Neubildung elastischer Fasern in der Intima bei Endarteritis," *Ziegler's Beiträge*, xxiv., 1898.

cells of formative tissue, or in myxomatous or fibrous connective tissue. When myxomatous tissue changes into fat tissue the star-shaped cells become globular fat-cells, while the intercellular mucoid material vanishes. The medullary tissue of bone may become changed into fat tissue—fatty marrow—in the same manner.

Myxomatous Tissue.—Myxomatous tissue may be produced from formative tissue by the appearance of a homogeneous, jelly-like intercellular substance which contains mucin, while the cells send out processes that form a network. It may also arise by metaplasia from any of the other connective tissues. When fibrous tissue changes into mucoid tissue the fibrillated intercellular substance disappears, and in its place appears mucoid material, while the connective-tissue corpuscles change into cells with interlacing processes. In an analogous manner cartilage, bone, and fat tissue may become transformed into myxomatous tissue.

Lymphadenoid Tissue.—Lymph-nodes are the seat of a constant physiologic regeneration of lymphocytes. After loss of substance or in pathologic new formations the endothelial cells and the cells of the connective-tissue framework proliferate; new reticulum is formed, in which lymphocytes and large endothelial cells accumulate.

HYPERTROPHY.

Hypertrophy is the increase in the size of an organ or tissue due to an increase in the size or in the number of its cells, or to both, without any appreciable alteration in its structure. As a general rule, hypertrophy depends upon an increase in the number as well as in the size of the cells of an organ or tissue. When it is due entirely to an increase in the size of the cells it is often denominated *true hypertrophy*; and when it is due to an increase in the number of the cells it may be designated as *numerical hypertrophy*, or *hyperplasia*. The existence of true hypertrophy can only be determined by painstaking micrometric measurements of the individual cells of the organ in question. As indicated, hypertrophy is accompanied by an increase in the size of the organ affected; in hollow organs, as the heart and urinary bladder, the increase in tissue may take place at the expense of the cavity enclosed (concentric hypertrophy). The most exact idea of the degree of hypertrophy present in an organ is obtained by comparing the weight of the organ with the normal standard. It is to be remembered that increase in size as well as in weight may depend upon many other causes besides hypertrophy, and consequently it is important to be sure that an apparently hypertrophic tissue possesses a normal structure.

Hypertrophies not dependent upon a congenital tendency to excessive growth usually result from an increase in the functional demands placed upon the organs and tissues. Such hypertrophies are therefore very properly spoken of as *labor* or *functional hypertrophies*; they are observed particularly in muscular and glandular organs. The physical and chemical changes in the muscle-cell or gland-cell incident to increased function in some way lead to cell growth (Welch). In certain diseases of the arteries—arteriosclerosis—there is a marked increase in the resistance to the blood-current, to overcome which the heart must increase the strength of its contractions; in stenosis of the valvular orifices, or in insufficiency of the valves of the heart, disturbances result in the mechanic apparatus of the organ that mate-

rially increase the labor necessary to maintain the circulatory equilibrium ; in these and similar instances the heart-muscle usually undergoes hypertrophy, and thus in a measure it fulfils the extra requirements placed upon it. By so doing, it compensates for the disturbances of the circulation produced by the vascular and valvular disease, and hence the hypertrophy is generally called compensatory hypertrophy.

Compensatory hypertrophy of the heart usually develops when there is necessity for it, provided the general condition of the nutrition is favorable ; it develops more readily in young than in old persons—facts illustrating the influence of functional increase, nutritive supply, and of age upon the growth and proliferation of cells.

Similar hypertrophy may develop under analogous conditions in the arteries, the uterus, the urinary bladder, the ureters, the stomach, the intestines, and the skeletal muscles. The uterus during pregnancy is the seat of an enormous hypertrophy, the increase in the size of the muscle-fibers being many times that of those of the nonpregnant organ. Moderate increase in the obstruction to the outflow of urine will be overcome by a compensatory hypertrophy of the bladder ; in narrowing of the pyloric orifice and in gradual intestinal obstruction the stomach and the intestines often become greatly hypertrophied. A persistent increase in the tension of the arteries has been shown by Thoma to lead to an increase in the thickness of the media.

Examples of compensatory hypertrophy are also frequently observed in connection with glands. Thus, if one kidney is destroyed, congenitally absent, or rudimentary, then the remaining kidney performs the function of both, and soon presents a greater or less degree of hypertrophy. In the case of congenital absence or marked hypoplasia of one kidney the remaining organ may increase to such an extent as to weigh as much as both kidneys together ordinarily do ; but if the loss of one kidney occurs after the growth of the body has been completed, then the hypertrophy of the remaining kidney is much less marked—another example of the greater power of hyperplasia of youthful tissue than of old. In the case of the kidney the compensatory hypertrophy has been shown by a number of studies (Grawitz and Israel, Nothnagel, and others) to depend in part upon a true hypertrophy, in part upon a hyperplasia of the glomeruli and uriniferous tubules.

When the liver sustains an extensive loss of substance, then the remaining portion undergoes hypertrophy. After extirpation of one adrenal there ensues hypertrophy of the other (Stilling). Compensatory hypertrophy of the testicles, ovaries, and mammary glands may occur (von Recklinghausen, Ribbert). After removal of the whole or part of the thyroid hypertrophy occurs in the remaining portion and in such accessory thyroid glands as may possibly be present, and in all probability also in the hypophysis (Rogowitzsch, Stieda)—a fact pointing to a functional relationship between the thyroid and the hypophysis.

Among other instances of compensatory or adaptive hypertrophy may be mentioned the great enlargement of the normal lung when its fellow has failed to develop (agenesia), and the extensive hypertrophy of the fibula when the tibia is rendered useless in the support of the body (Sutton).

Hypertrophy (hyperplasia) of the lymph-glands, the lymphadenoid tissue in general, and of the spleen (leukemia), and also of the thyroid gland (goiter), occurs under conditions for which we have as yet no very definite explanation.

Tissues subject to constant wear may become greatly increased in size when, for any reason, the continual loss of substance ceases. Overgrowth from lessened waste occurs especially in connection with the dermal organs, such as the nails, hair, and teeth. If the wear of the nails be prevented, as in bedridden patients, they are sure to attain considerable proportions (hyperonychia, onychogryposis) (Fig. 46). Similar overgrowths are observed in the horny portions of the feet of animals, the beaks of birds, and the teeth of rodents. According to Sutton, the growth of the incisor teeth of rodents is unconditional, unless held in check by constant usage. They may grow to excessive length under any of the following conditions: 1. Slight mobility of the tooth in its socket. 2. Diminished usage, as when rodents are in captivity. 3. Loss of antagonism of the teeth, either from fracture of a tooth or injury to the maxillæ, leading to displacement of the parts (Fig. 47). The great overgrowth that follows may lead to perforation of the skull. The tendency of these teeth to grow in a circle is explained



FIG. 46.—Overgrowth of the nail of the big toe in a bedridden person.

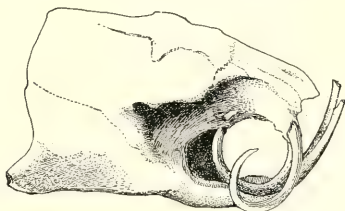


FIG. 47.—Overgrowth of the incisor teeth of a wood-chuck, due to loss of apposition on account of fracture of the lower jaw.

as due to the fact that in gnawing the posterior part of the teeth yields first, the anterior hard coating of enamel being the last to yield (Sutton).

Among overgrowths of congenital nature are the so-called giant growth, in which the body reaches an excessive size, and partial giant growth, in which one extremity, one finger, or some other portion of the body presents a relative excess in bulk. Similar overgrowths may occur in special tissues, as the skin or its appendages (ichthyosis, hypertrichosis), in bones (acromegaly), etc. Overgrowths of this kind must be ascribed to conditions depending either upon an excessive number of cells, upon the presence of cells with an exaggerated tendency to multiply, or upon the absence of the influences that ordinarily restrain the growth of tissues.

INFLAMMATION.

THE STUDY OF THE REACTIONS OF THE ORGANISM TO INJURY.

Introduction.—The exact significance of the word inflammation cannot be compressed into the narrow frame of a dogmatic definition. The views held of the limitations of the term inflammation vary. As will be seen from a perusal of the descriptions in this book, inflammation is a complex local process composed of disturbances of the circulation, of retrogressive and progressive changes, associated in varying degrees, and initiated by a variety of injuries. The general consideration of the nature of these processes at

one time, under the heading of inflammation, is warranted by reason of their common mode of origin. The external, obvious manifestations of the process may vary according to the kind of tissue and the intensity of the changes; but close examination shows that in each case virtually the same succession of changes follows the action of different causes. The comparative study of the action of injuries throughout the animal kingdom has shown that the same general principles underlie the resulting phenomena in the cells and tissues. Hence it will suffice for the present to regard the inflammatory changes as the local reaction of the tissues to injuries and lesions of various kinds. Herein is implied that some, at least, of the changes diminish the effects of the injury; that the reaction is salutary.¹

EXPERIMENTAL INFLAMMATION—THE STUDY OF THE REACTION TO INJURIES IN ANIMALS.

Metschnikoff² and others have shown that unicellular organisms rid themselves of foreign particles either by solution, through the action of digestive vacuoles containing an acid ferment, or by extrusion; and that losses of substance are readily repaired provided the nucleus persists.

In multinuclear organisms the reaction becomes more and more complex. In the echinoderms Metschnikoff found that when the epiblast is punctured by a foreign body, wandering mesodermal cells move toward the foreign body, attach themselves to it, and fuse into plasmodial masses, the function of which seems to be to isolate and remove foreign substances. Smaller bodies, such as living bacteria, are digested by single mesodermal cells, which ingest the bacteria by sending out pseudopods. Such cells are also known as *phagocytes*. This reaction is in no way influenced by the nervous or vascular system. The remarkable power of repair in the lower *Metazoa* is well seen in the *Hydra*, which may be divided into several pieces, from each of which a new individual is formed.

Among the *Metazoa* with an incomplete vascular system it has been shown that leukocytes move actively toward regions of injury or infection, and surround foreign bodies that are present; many of the leukocytes act as phagocytes, incorporate and digest small particles; others are not phagocytes, but contain granules that stain with acid dyes, and that are readily extruded; of the fixed cells, the endothelial cells especially may act as phagocytes.

In the higher animals the simplest conditions after injury are furnished by the avascular tissues, such as the tail-fin of the young axolotl and newt, or the cornea in higher forms. By depositing with a needle a few grains of carmin in the tail-fin of the axolotl a certain number of cells are destroyed, and the living cells in the immediate vicinity become swollen and vacuolated; wandering cells in the spaces between the fixed cells move toward the area and take up the grains of carmin and the cellular detritus, while the epidermis folds over and covers the wound; this is followed by regeneration of the lost cells and the return of the tissue to its normal state. In this course of events the vessels need not take any part whatsoever.

The course of inflammation in the cornea has been studied repeatedly, and

¹ For full references to recent literature on inflammation, consult J. George Adams's article in Allbutt's *System of Medicine*, i., 1896.

² *Pathologie comparée de l'Inflammation*, 1892.

with the most diverse results ; but the correctness of the following statements cannot be questioned. The cornea is perfectly avascular ; it is composed of fibers ; between them is a network of spaces, bathed with lymph, in which lie the corneal cells. When a small area of the anterior surface is destroyed by means of zinc chlorid or other caustic agent, a small opacity soon forms, due to the accumulation of leukocytes about the injury. The leukocytes move actively into the area from the lymph-spaces in the cornea itself and from the lacrimal fluid bathing the conjunctiva. The next step consists in the regeneration of the cells originally destroyed. When a small quantity of a bouillon suspension of the *Staphylococcus pyogenes aureus* is brought into the cornea with a needle, a few of the corneal cells about the cocci are killed ; as the cocci multiply the necrosis extends, and at the same time leukocytes are attracted toward the area and fill the lymph-spaces in its vicinity. In such experiments the reaction may extend to the vessels at the corneal margin, which become dilated and congested, the leukocytes passing through the vessel-walls and toward the micro-organisms. The leukocytes take up some of the cocci into their interior, where the cocci may perish ; but it is equally possible that the leukocytes may die in consequence of the action of the cocci, and, if the latter are relatively virulent, extensive necrosis and loss of corneal substance may ensue—an ulcer forms. Sooner or later as the cocci die the extension ceases. In the mean time leukocytes accumulate more and more in the corneal spaces ; vascular sprouts grow into the cornea from the margin ; and finally processes of proliferation of the corneal cells and definitive repair begin (Councilman).¹

In vascular tissues the inflammatory reaction reaches the highest degree of complexity, but gradations in the process from the mild to the more intense are observed. Uncomplicated aseptic incisions heal with a minimum of reaction. Some reddening of the margins of the wound, due to congestion of the vessels, and the formation of a thin fibrinous layer on its surface, usually take place, and a few leukocytes wander out into the margins of the injured spot ; but the main role is played by the fixed cells, which enlarge and send out processes that may interlace, at the same time as new cells are formed to replace those destroyed ; new capillaries are also formed. The changes here are essentially regenerative.

A general survey of the events in acute inflammation of a vascular tissue is best obtained by studying the changes that occur in such transparent parts as the tongue, the mesentery, and the web of the frog, and the mesentery of rabbits and other warm-blooded animals, after injury. Such experiments were first made by Cohnheim in 1867. It has been found that the acute inflammatory changes are the same in virtually all vascular tissues, including those of man. In some of the tissues experimented with, it is necessary to apply a chemical irritant or to produce a slight loss of substance in order to induce reactive changes ; in others, as, for instance, the mesentery of the frog, mere exposure to the air is sufficient. A curarized frog is taken, and an incision is made in the left flank, through which a loop of small intestine is carefully drawn out, and fastened by means of pins to strips of cork glued to a glass slide, or it is merely stretched over a glass cube fastened to a glass plate in such a manner that a portion of the mesentery is conveniently arranged for microscopic examination ; or the web of a

¹ The character of the exudation in acute keratitis of the rabbit, *Tr. Chicago Path. Soc.*, 1900, iii., 68-85.

small frog may be taken, a small piece of the skin nipped off, and the subsequent changes studied under the microscope.

In such experiments it will be seen that the blood circulates through the vessels in two distinct currents, namely, the central, or axial, containing the red and white blood-corpuscles, and the marginal, peripheral, or plasmatic current, which ordinarily is free from corpuscles. Very soon after the exposure of the mesentery dilatation of the arteries with increased rapidity of the current follows—an active hyperemia—and dilatation of the veins and capillaries gradually ensues, and the current becomes slowed. As the current becomes slower the leukocytes accumulate in the plasmatic zone in the veins, while in the capillaries the red and white corpuscles are mixed irregularly. The circulation in the capillaries becomes disturbed; now it stops, then it moves on again, only to stop for a little longer time; the number of leukocytes in the capillaries also seems to increase in proportion to the red cells. The distinction between the marginal and the central zones in the veins is soon lost, and the corpuscles gather near the walls of the veins. Individual leukocytes apply themselves very closely to the inner surface of the vessels; soon a small projection appears on the outside of the capillary or vein; while this projection grows larger the intravascular part of the cell grows smaller, until the whole leukocyte lies outside of the vessel, and perhaps moves away from it by means of active ameboid movements. The leukocytic emigration may be very marked. In the meantime the dilatation of the vessels and the slowness of the current may have become extreme, so that in some vessels there is almost complete stasis. Red corpuscles may have been pressed out into the tissue either by diapedesis or rhexis. At the same time it is evident that considerable plasma has exuded into the tissues, and, becoming mixed with broken-down leukocytes, it may give rise to the precipitation of fibrin, whereby the field becomes more and more obscure, as if covered with a fibrinous deposit.

Such observations as the above may have to be prolonged for hours in order that all the details outlined here may be studied.

The subsequent events it is practically impossible to follow by continuous observation under the microscope. Suffice it to say that the leukocytes may disintegrate or wander away, that the vessels may return to their normal caliber and the current be re-established, while rapid cell proliferation points to active repair; or micro-organisms may enter the tissues and cause extension of the process. The microscopic examination of properly fixed and prepared tissues that during life were the seat of inflammation is the principal method of study of the successive stages of the retrogressive and progressive changes in the farther stages of the process; and it has been learned that the proportion of the various constituents of the blood in the exudate, as well as the nature of the changes in the fixed tissues, varies greatly in different instances of inflammation.

These brief considerations will serve to emphasize that the same general principles underlie in all animals the reactions to injuries. In the lower animals wandering cells play the principal part in ridding the organism of injurious substances. In the higher animals the accumulation of leukocytes and wandering cells in the injured area is a constant and perhaps the most striking feature of the inflammatory reaction. In vascular and, to a certain extent, about avascular tissues important changes in the blood-vessels occur that lead to exudation and favor leukocytic emigration. Later phases of

the process, namely, proliferation of fixed cells and repair, are closely connected with the early reactive changes, and both sets of phenomena may be regarded as stages of a single process.

THE FACTORS IN THE INFLAMMATORY PROCESS.

On account of the intricate structure of the principal tissues in the higher animals a number of distinct factors take part in the inflammatory process. The parts taken by the vessels, the nervous system, the leukocytes, the exudation, and the fixed cells all demand consideration.

The Vessels in Inflammation.—Cohnheim regarded the changes in the vessel-walls as of fundamental and primary importance in inflammation. The exact nature of the changes could not be explained, but alterations took place that resulted in increased porosity or permeability, allowing plasma and corpuscles to pass through. The study of the role of the leukocytes in inflammation, of the action of the serum, of the adaptive tendency of the whole process, has profoundly modified this early conception.

Nevertheless, distinct alterations of the structure of the walls of the vessels are thought to occur in inflammation, principally because the composition of the exudate corresponds closely with that of the blood-plasma, thus pointing directly to an increased permeability. Such alterations are not always morphologically demonstrable; they may exist in the cement substance between the cells, where changes are usually seen after inflammation, the traces left by the migrating leukocytes being quite distinct in silvered preparations. Whether the alterations in the vessel-walls are altogether passive and due to the lesion produced by the harmful agent, such as pathogenic micro-organisms, or whether they are active and purposive, due to contractions of the endothelial cells which open the pores between them, so as to allow the passage of blood-cells and blood-plasma, cannot be stated precisely. In severe inflammatory lesions the walls of the blood-vessels may suffer retrogressive and passive changes that increase the porosity and lead to circulatory disturbances; they may be torn on account of the violence of the hyperemia or by the necrotic action of toxic substances on the cells. Stricker, Klebs, and others have found that the endothelial cells are contractile and may change their position: this property must play an important part in the formation of stomas in inflammation. It is therefore not improbable that some of the alterations in the vessel-walls are active processes which facilitate the leukocytic migration and serous exudation. Leukocytes are, however, fully able to traverse normal walls.

The endothelial cells are not only contractile, but also, according to Metschnikoff, phagocytic and mobile. This is true also of the lymphatic endothelial cells and of the cells lining serous membranes. Thus, tubercle bacilli, malarial organisms, and various other microbes, as well as different substances, such as pigments, are frequently taken up by endothelial cells, especially those of the liver. Inasmuch as some of the micro-organisms are immobile, their presence within the protoplasm of endothelial cells must be attributed to an active cellular process.

In agreement with these functions, the endothelial cells in inflammation frequently enlarge and project into the lumen of the vessel, causing an increased resistance to the blood that tends to slow its rate of flow; the nuclei of the cells also stain more deeply, and mitosis may occur; in many

acute and chronic inflammations intravascular and other proliferation often takes place, and is usually traceable to the endothelium. Moreover, in regenerative and other proliferations the endothelial cells, by budding, give rise to new capillaries.

Whether the secretive function claimed by Haidenhain for normal endothelial cells influences the composition of the exudate in any way has not been determined. By the addition of substances derived from disintegrating cells the composition of the exudate becomes greatly altered after it leaves the vessels.

The Influence of the Nervous System in Inflammation.—

In former times vasomotor disturbances, either in the sense of paralysis (Henle) or of spasm (Brücke), were regarded as the essential causes of the whole process of inflammation. Cohnheim demonstrated, by cutting all the tissues connecting the tongue of a frog with the body, with the exception of the artery and the vein, that acute inflammation proceeded in a fairly typical manner without the intervention of central nervous influences.

Ordinarily the nervous system exercises a direct influence on the inflammatory process. Samuel showed that if the sympathetic (vasoconstrictor) is divided on one side, and the auricular branches (vasodilator) on the other side, there is a marked difference in the inflammatory reaction in the ears of the rabbit when they are placed in water warmed to 54° C. The ear the sympathetic of which has been cut manifests an acute inflammation proceeding rapidly to recovery; whereas the ear deprived of the vasodilator influence becomes the seat of stasis without hyperemia, and necrosis finally ensues. Similar results were obtained by Roger after injecting cultures of the streptococcus of erysipelas into ears under the same conditions. In the ear the auricular nerves of which had been cut the erysipelatous inflammation lasted long and mutilation resulted; on the side with the sympathetic divided the inflammation ran a more rapid course to recovery. These experiments indicate clearly the influence of nerves on inflammation. The uncontrolled action of the vasoconstrictors interferes with hyperemia and exudation; the noxious substances are not removed; repair is delayed. Under the action of the vasodilators the stages are hastened and rapid recovery follows.

The powerful influence of the nervous system is also shown by the fact that hypnotic suggestion may be followed by at least some of the local symptoms of acute inflammation.

The Leukocytes in Inflammation.—The Leukocytic Emigration.

—One of the most striking features in inflammation is the peripheral disposition and the emigration of the leukocytes. The emigration of leukocytes was first observed by Dutrochet in 1828. Gulliver in 1842 compared the cells in pus to leukocytes. Addison in 1843, and Waller again in 1846, demonstrated the emigration of leukocytes, but these observations were forgotten until Cohnheim discovered the process anew in 1867.

As already observed, the blood-corpuscles are normally carried along in the axial current of the circulating blood, while the marginal zone is almost wholly plasmatic. The red corpuscles are found in the center and the white cells in the peripheral parts of the axial stream. The cause of this arrangement of the cells in the current has been shown by Schklarewsky and D. J. Hamilton to depend upon the relative specific gravity. When small bodies of different specific gravity are made to circulate in fluids through a series

of tubes, it is found that the heavier bodies run in the center of the stream, and the lighter bodies—in the case of the blood, the leukocytes—tend to gather in the marginal zone. When the current becomes slow the heavier bodies—the red cells—also pass into the periphery of the stream, and the axial character of the current is lost. While the slowing of the current in inflammation undoubtedly favors the peripheral arrangement of the cells, it does not fully explain the characteristic margination or “peripheral drift” of the leukocytes, which does not occur in merely delayed flow. As the leukocytes in inflammation reach the peripheral zone of the plasma-stream they move backward and forward for a little time (Landowsky); but soon they attach themselves to the wall, spread themselves out in close contact with it, and finally passage through the wall—emigration—follows (Figs. 48 and 49).

Arnold and others have shown by silvering the outlines of the endothelial cells that the emigration occurs through the cement that holds the cells together; after emigration the silver lines are broader, and present circumscribed pores that are regarded as traces left by the migrating cells. According to Löwit, emigration may even occur without any changes in the

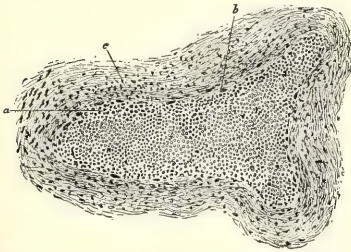


FIG. 48.—Acute inflammation of the mesentery following necrosis of the vermiform appendix on account of the impaction of a fecal concretion: *a*, peripheral accumulation of leukocytes and emigration through the vessel-wall (*b*) and perivascular accumulation (*c*). Hematoxylin and eosin. $\times 175$.



FIG. 49.—The same as Fig. 48, but with higher power: *a*, leukocytes accumulating near the wall; *b*, endothelial line; *c*, leukocytes in the act of passing through the vessel-wall; *d*, perivascular accumulation of leukocytes. $\times 350$.

cement; and Engelmann found that leukocytes may even pass through the bodies of the endothelial cells.

The further movements of the leukocytes outside of the vessels are also of an active nature. They may wander in fairly straight lines to lymphatics, which they have been seen to enter by passing between the endothelial cells (Hering, Heller, Thoma). More frequently they move in a definite direction, as if by a prearranged understanding; this is seen very plainly in the accumulation of leukocytes around the lesion of the cornea in keratitis; in many other inflammations the leukocytes build a wall or ring around some central point.

Chemotaxis.—At first Cohnheim regarded the migration of leukocytes as an active process, but subsequently he coincided with Hering and Schklarewsky in the belief that the cells were merely pressed through the altered walls of the vessels. Taking, however, the facts above mentioned into consideration, it seems that leukocytic emigration is something more than a passive process. This inference has long ago been shown to rest on a substantial basis by the demonstration that chemical substances exert

a profound influence on mobile cells. This influence, which may attract or repel cells, is known as positive or negative *chemotaxis*. Engelmann showed that certain motile bacteria are attracted toward points where oxygen is present. Pfeffer demonstrated that myxomycetes, infusoria, and swarming spores are drawn toward some substances and repelled by others; further, that the power of attraction or repulsion does not bear any relation to the molecular weight or food-value of the substances. Leber, Massart and Bordet, Gabritschewsky, Buchner, and others have made similar observations on leukocytes. It has been shown that the behavior of these cells toward stimulating substances varies greatly, and that chemotaxis plays an essential role in the migration of these cells in inflammation.

The experiments bearing on this point have been carried on by inserting into the tissues of animals capillary tubes filled with certain substances, and then observing to what extent leukocytes would creep into the tubes. Leukocytes are drawn toward the majority of bacteria that induce inflammation, but repelled or destroyed by a few that are especially virulent. Bacterial products also attract leukocytes; and Buchner found that the bacterioproducts—the substances of the bodies of the bacteria—and many of the early products of tissue disintegration exert an attraction upon cells. Leber and others showed that croton oil, turpentine, copper, etc., exert positive chemotaxis; while quinin, chloroform, alcohol, lactic acid, etc., manifest negative chemotaxis. Some of these latter substances were known to suspend ameboid movement (Binz, Pekelharring) before chemotaxis was understood, and they were then referred to as protoplasmic poisons.

Thoma has demonstrated that when the amount of salt in the blood and lymph of the frog is increased to about 3 per cent., the movement of leukocytes and wandering cells is arrested. In warm-blooded animals emigration was stopped by irrigating the mesentery or tongue with a 1.5 per cent. salt solution; the ameboid cells became immobile and globular, and those adherent to the vessel-wall were loosened; but if irrigation was made with a 0.75 per cent. solution, migration and ameboid motion were resumed.

Bouchard, Roger, and Ruffer have shown that the introduction of a micro-organism, such as *Bacillus pyocyaneus*, or its products, into the circulation prevents or delays emigration after the local injection of substances that usually cause marked accumulations of leukocytes; exudation occurs, but the white cells remain within the vessels.

These experiments indicate that the influence of substances in solution varies according to the state of concentration and distribution. The even distribution of bacterial products in considerable quantity in the blood, for instance, may materially diminish the leukocytic emigration toward similar substances collected at a local seat of disease. In some such way may be explained the marked variations in the leukocytic reactions in different inflammations due to the same cause.

Sometimes one variety of leukocytes emigrates in relatively larger numbers than the others, as, for instance, in the skin in dermatitis herpetiformis, in which the eosinophiles gather in large numbers. This indicates that the sensibility toward chemical substances is peculiar for each kind of leukocyte.

The active movements of the leukocytes and wandering cells in inflammation depend, then, on chemotaxis exerted by the diffusible products of bacteria, of tissues, and of other substances. The changes in the vessel-walls, the modification of the endothelium, the vascular dilatation and slow-

ing of the current, and the disarrangement of the corpuscles in the stream, all favor emigration; but the determining factor is the presence of chemotactic substances in the tissues and the vessel-wall, in consequence of which the cells advance, as long as the ameboid motion is intact, toward the points of greatest attraction.

As regards the passage of red corpuscles from the vessels, which may occur to a considerable extent in some inflammations, it is to be noted that it generally succeeds the leukocytic emigration save in those cases in which there is a severe or gross injury to the vessels. White and red cells may be seen lying side by side along the walls of the vessels of the frog's mesentery, but the leukocytes are always the first to emigrate. It is quite clear that the continued active emigration of leukocytes increases the permeability of the walls, so that after a time red corpuscles may be forced through. When the circulatory disturbances become severe, so that stasis ensues, red cells often leave the greatly altered vessels in large numbers, giving the inflammatory exudate a hemorrhagic character.

Phagocytosis.—Metschnikoff introduced the now well-known word phagocytosis to describe the action of cells, especially certain leukocytes and wandering cells, of taking up into their interior pathogenic bacteria and other particles, and of destroying them by a process of intracellular digestion. The leukocytes possessed of this function are the finely granular neutrophile and oxyphile cells (polymorphonuclear leukocytes) and the large mononuclear hyaline cell; endothelial cells and other fixed mesoblastic cells have the same property, but exert it to less degree.

Phagocytosis is largely dependent on positive chemotaxis on the part of the micro-organisms or their products and other substances. The phagocytic leukocytes vary in their action toward different bacteria. Metschnikoff says that in man the hyaline cell does not take up gonococci, which are readily taken up by the finely granular oxyphile cell; this cell does not, however, take up leprosy bacilli, which are engulfed by the hyaline leukocytes. Such differences must depend on varying sensibility on the part of the leukocytes to micro-organisms.

Leukocytes that by virtue of chemotaxis are attracted by bacteria and other particles move toward the bacteria and particles and enclose them in their protoplasm. Subsequently the ingested substances undergo various changes that are ascribed to intracellular digestion. Ferments have been shown to be present in the cells. Leber showed that sterile pus, the result of the accumulation of leukocytes in the anterior chamber of the eye after the insertion of copper, could digest fibrin. Pus-cells, bits of muscle, and other tissue fragments taken up by the phagocytes disintegrate and become dissolved. Ingested microbes present changes in form and in affinity for stains; frequently the degenerating bacteria lie in so-called digestive vacuoles. The exact nature of the bactericidal substances or ferments is not determined.

Metschnikoff concludes that some bacteria must be in a living condition when taken into the cells, because certain bacilli have been observed to perform active movements in the nutritive vacuoles of the leukocytes; again, on introducing leukocytes filled with anthrax bacilli into bouillon the cells fall to pieces, while the bacilli grow rapidly; and it is quite likely that the tubercle and leprosy bacilli found in phagocytes were fully virulent and living when incorporated by the cells. But the incorporation of micro-

organisms by phagocytes does not always or necessarily lead to death of the bacteria; their products may, on the contrary, destroy the phagocytes, so that in many cases the disease progresses rapidly in spite of well-marked phagocytosis. In other cases, as in tuberculosis, leprosy, and glanders, the resisting powers of the bacteria and of the cells are more evenly balanced, and the chronic course as well as the localized form of these diseases has been explained by this peculiarity; in such instances the bacteria may multiply within the cells. The more virulent the bacteria, the less marked, as a general rule, is the accumulation of leukocytes and the phenomenon of phagocytosis. Metschnikoff describes a striking example of the action of bacteria of differing virulence: if an attenuated culture of the bacillus of anthrax is inoculated into the ear of a rabbit, a huge aggregation of leukocytes with vigorous phagocytosis results; but if a virulent culture is injected, an intense serous inflammation follows, the fluid of which contains but few leukocytes—the virulent bacteria repel or kill the leukocytes, the weak attract them. In many instances the ingestion of bacteria or of chemical substances, as arsenic (*Besredka*), is first followed by negative chemotaxis, which later gives way to positive chemotaxis and phagocytosis.

Buchner, as already mentioned, demonstrated that some of the products of tissue disintegration exert marked attraction on leukocytes; this may explain the immigration of leukocytes into practically all areas in which lesions of any kind have produced cell death. The function of the leukocytes in aseptic inflammations, as well as in bacterial inflammations after the active agent has been destroyed or neutralized, is largely to assist in the removal of débris, partly by phagocytosis, partly by carrying the detritus to lymph-nodes and other organs. This is well illustrated in fibrinous pneumonia; after healing begins the peribronchial glands become enlarged and filled with débris from the exudate in the alveoli, brought partly by the lymph-stream, partly by leukocytes migrating from the area involved.

Leukocytes are useful in yet another way, namely, by supplying the formative cells with nourishment; the formative cells under such circumstances appear to act as phagocytes and incorporate the white blood-cells. The question concerning the conversion of migratory cells into fixed-tissue cells is referred to below.

The Extracellular Action of Leukocytes.—While Metschnikoff and his followers looked upon leukocytic emigration and phagocytosis, or the intracellular action of the leukocytes, as the essential element in the inflammatory reaction throughout the animal kingdom, and regarded the vascular, exudative, and other phenomena in inflammation in the higher animals as superadded and auxiliary steps, many facts indicate that this is rather an incomplete conception of the inflammatory process, and that the extracellular action of the leukocytes and the properties of the exudate play at least an equally essential role.

Nuttall was among the first to show that blood-serum has a marked bactericidal effect; attenuated anthrax bacilli, for instance, when placed in normal serum show involution and degeneration forms before they are taken up by phagocytes. This permits the inference that phagocytosis may occur after the inflammatory exudate has reduced the vitality of the bacteria. The demonstration of a microbicidal action of the blood-serum has been abundantly confirmed (*Nissen*, *Buchner*, *Hankin*, *Behring*, and many

others); and further investigations in the same direction have led to results of supreme practical importance in showing the existence of antitoxic substances in the blood of animals immune to certain diseases. But the discussion of the production of immunity—one of the most interesting topics in biology—does not belong here. Certain facts pointing to the local action of leukocytes in producing bactericidal substances must, however, be detailed.

Nuttall and others found that the serum removed from the body possessed more bactericidal power than the blood; Buchner showed that the injection of sterile emulsions of wheat gluten into the pleural cavity produced a sterile exudate remarkably rich in leukocytes and more strongly bactericidal than the blood of the animal, and this bactericidal power was retained after the leukocytes had been killed by freezing and thawing, so that phagocytosis could not possibly play any part. Experiments of similar import, pointing to the production or liberation of bactericidal substances by the leukocytes, have been made by Denys and Havel, and others. Vaughan and Kossel demonstrated the presence in the blood-plasma of nucleinic acid, a bactericidal substance found only in nucleated cells. Löwit was able to extract from leukocytes a strongly bactericidal body, and demonstrated that on ligating the aorta, so as to prevent the entrance of leukoblasts from the hemopoietic organs into the circulating blood, a marked lessening in the bactericidal power of the blood took place with the diminution of polynuclear leukocytes. These facts point strongly to the production of bactericidal substances, or *alexins*, as Buchner calls these protective bodies, by the leukocytes, through a process either of secretion or disintegration. It would seem that in inflammation the emigrating leukocytes, even though they may be destroyed and undergo dissolution, nevertheless hinder bacterial growth by the setting free of bactericidal substances contained in their bodies. Active processes of secretion of alexins on the part of the leukocytes may also occur (Hardy). In these ways the composition and action of the exuded serum may be profoundly changed.

Metschnikoff, while not denying the bactericidal action of blood-serum outside the body, *in vitro*, has persistently maintained that no conclusions can be drawn as to the events that occur in the living organism from the results obtained in experiments with serum outside the body. The pathogenic bacteria, he maintains, are destroyed by the phagocytes. Possibly the serous exudation may serve to attenuate or modify the action of the poisonous chemical products of the bacteria which produce the general intoxication in inflammations. Other observations point to important extracellular processes in the inflammatory reaction. Thus, Afanassieff found that on placing virulent cultures of anthrax bacilli on healthy granulation-tissue a rapid destruction of the bacilli by the serum followed before phagocytosis had time to occur; later the identical degenerate bacillary forms were found outside as well as inside the phagocytes. R. Pfeiffer showed that when cholera spirilla are inserted into the abdominal cavity of refractory guinea-pigs the spirilla become swollen and spheric before phagocytosis has time to occur. Metschnikoff repeated this experiment, and observed that a few minutes after the injection the leukocytes were surrounded by free globular spirilla, a layer of clear fluid separating the cells from the bacteria; here he acknowledges that an extracellular action of the leukocytes takes place.

Furthermore, not all leukocytes are phagocytes. The eosinophiles, or coarsely granular oxyphile cells, never act as phagocytes, yet they are often

present in relatively large numbers in inflammatory exudates. What is their possible function? Kanthack and Hardy observed that on mixing anthrax bacilli with frog's lymph the coarsely granular oxyphiles were attracted and applied themselves to the bacilli; the granules were then discharged, and the bacilli soon showed signs of degeneration and became surrounded by hyaline cells fusing into plasmodial masses which subsequently broke up, the cells containing remnants of bacilli within digestive vacuoles. Hardy has shown that the same phenomena occur on placing *Bacillus filamentosus* in the lymph of the frog. Such observations point clearly to excretory functions on the part of nonphagocytic cells. Kanthack and Hardy found further evidences of this secretory function in various warm-blooded animals as well as in man; similar phenomena were observed in hanging drops of human blister fluid mixed with anthrax bacilli. Hence it may be concluded that the extracellular action of leukocytes is of much importance in inflammation.

Conclusion.—From these considerations it may be concluded that chemotaxis and leukocytic emigration are important and practically constant steps in the inflammatory process; that the action of the polynuclear and hyaline leukocytes is partly phagocytic; that the eosinophile cells are not phagocytic but excretory, and may diminish the vitality of micro-organisms; and that the disintegration of leukocytes increases the bactericidal powers of the serum in the inflammatory area.

The Inflammatory Exudates.—The inflammatory exudate varies in quality and quantity according to the tissues concerned and the nature and intensity of the inflammatory agent. Dense tissues allow but little exudation to take place, while vascular structures without much resistance—*e. g.*, cutaneous and serous surfaces—readily permit much exudation.

The exudates are invariably richer in proteids than ordinary lymph. Whether this is due to increased permeability of the vessel-walls, to the disintegration of cells, or to stimulation of the secretory activity of the endothelium, is an undecided question. The exudates also frequently contain fibrin and its precursors, digestive ferments and peptones, bactericidal substances, and various cells.

The **serous** exudates occur chiefly in milder forms of inflammations, but also in certain very virulent infections; *e. g.*, with anthrax bacilli. The fluid contains little or no fibrin, only a few cells, but more albumin than the transudates. Serous exudates act favorably by irrigating the tissue-spaces and removing or diluting noxious substances; the exudate also brings increased nourishment to the cells, thus favoring reparative cell growth; but in all likelihood its most important effects are attributable to bactericidal substances produced by leukocytes and possibly by other cells (see *Extracellular Action of Leukocytes*). But the exudate may become a dangerous element in inflammation; it may carry bacteria away from the original focus to adjacent or contiguous structures, such as healthy parts of serous membranes, and through the lymphatics to lymph-nodes, where new areas of inflammatory reaction may be established. Accumulations of exudate in the tissues about the entrance to the larynx may cause asphyxia, and in the spaces of the meninges cerebral compression.

Serofibrinous and fibrinous exudates consist, as the terms indicate, either of mixtures of fibrin and serum or almost wholly of fibrin. Such exudates may form in the tissue-spaces, in the serous cavities, and on the

mucous and, more rarely, the cutaneous surfaces. The ferment necessary for fibrin formation is undoubtedly liberated by the disintegration of leukocytes, red corpuscles, and other cells. The fibrin may be precipitated in filamentous and hyaline form from pre-existing serous exudates, or it may be deposited directly upon the tissues at the moment the plasmatic fluid exudes from the vessels; in the latter instance the fluid comes in contact with cells, such as the lining cells, that are undergoing necrosis with the setting free of ferment, the fibrin forming a granular or velvety deposit or a thick membrane on the roughened surface. In serous cavities fibrinous exudates often appear to restrict the spread of the disease. In the peritoneum, for instance, fibrinous adhesions between intestinal coils often confine the infection about the region of its origin, such as the vermiform process or the uterine appendages.

The **hemorrhagic exudate** is due to a considerable diapedesis of red corpuscles, giving the fluid or the tissue infiltrated a bloody appearance. Such exudates signify extensive changes in the walls of the vessels, due either to the intensity of the primary lesion or to nutritive disturbances that have weakened the capillaries.

The **purulent exudate**, or **pus**, is a yellowish, milky or creamy fluid containing many cells, but no fibrin. Its peculiarities are due to disintegration of the proteids, the fibrin, and the necrotic tissue by ferments developed from pyogenic bacteria, as well as from cells. The study of the common pus-producing bacteria outside of the body, in pure culture, has furnished abundant proof of the development of ferments that peptonize gelatin and proteids. Leber showed that copper inserted into the anterior chamber of the eye produced a sterile pus capable of digesting proteids. The cells in the purulent exudate are chiefly polymorphonuclear leukocytes, which are attracted in large numbers by the bacterioproteins of the pyogenic micro-organisms (Buchner), by chemical substances, as well as by products of tissue necrosis. Formative cells that succumb to the toxins may also become pus-corpuscles; but in comparison with leukocytes this type of cells takes but a small part in forming pus-cells. As the leukocytes die the cytoplasm becomes granular and fatty, the nuclei are split up into fragments, and complete disintegration may take place. The necrotic tissue and the solid exudate that may have formed in the early stages are liquefied by the proteolytic ferments, and abscess cavities, ulcers, and suppurating wounds result. The pus micro-organisms are to be found in the pus-cells and in the plasma, as well as in the fixed and formative cells, especially in acute processes. The serum of pus contains the same salts as blood-plasma; furthermore, ferments, peptones, and bactericidal substances, and, if old, cholesterin crystals and fat, and also pigment from red blood-cells and from chromogenic bacteria.

The digestive action of the purulent exudate aids in the removal of dead tissue by dissolving and rendering the material susceptible of absorption or separation; but suppuration is to be looked upon as an unfavorable form of infection: it always causes local destruction of tissue and frequently tends to progress.

The Fixed-tissue Cells in Inflammation.—The changes in the fixed tissue in inflammation are partly *retrogressive*, partly *progressive*. These two kinds of changes are often closely associated. In many inflammatory areas the retrogressive changes are found in and near the center,

while proliferation occurs at the periphery. The retrogressive changes are usually more pronounced in the early stages of acute inflammation, while the progressive changes predominate when actual healing begins. There are many inflammations, however, in which cell growth is among the very first phenomena.

The inflammatory agent, of whatever nature—traumatic, chemical, or bacterial—in its first action on the tissue produces certain lesions. There may be necrosis and degeneration of cells; but in order that inflammation may take place the circulation in the vessels must continue. When the primary injury causes immediate death of an area the circulation ceases, reaction cannot take place—dead cells do not react. Hence immediate death in consequence of the primary intensity of the injury is in reality a phenomenon foreign to inflammation; inflammation occurs in the tissue around the necrotic area because here the injury has not suspended the vitality of the cells. It must therefore be apparent that inflammatory reaction follows injuries that produce lesions short of complete necrosis or death of the part.

As the inflammation progresses the fixed cells may be further damaged in various ways. The continued action of the inflammatory agent—*e.g.*, pyogenic and other bacteria—may produce necrosis and necrobiosis of the fixed cells and of the leukocytes. Necrosis may occur on account of the accumulation of toxic chemical products in a tissue the seat of inflammation, on account of the violence of the inflammatory vascular reaction, which may lead to stasis or thrombosis and anemia, and on account of the pressure of the inflammatory exudate that crowds into the tissue-spaces. In milder inflammations the same or similar causes may induce changes in the cells, leading to functional disturbances, and sooner or later to cell death and disintegration. Cloudy swelling and fatty degeneration are frequently observed in the parenchymatous as well as wandering, in new as well as old, cells; when the serous exudate infiltrates a tissue the fluid may soak into various structural elements, such as nerve-fibers and muscle-fibers as well as cells, and cause dropsical vacuoles; mucoid degeneration is frequent, especially in so-called catarrhal inflammations. Degenerations of obscure nature also take place in the intercellular substance, which may change into mucus, or swell up, soften, and disappear. In the myocardium, for instance, the intercellular cement may change so that the muscle-fibers undergo segmentation—*i. e.*, separate into the cells or segments of which they are made up. Hyaline and amyloid degenerations occur in chronic inflammations. Such changes are essentially destructive.

In some inflammations the cell degeneration, like cloudy swelling, fatty and mucoid changes, is associated with proliferation. This is seen in catarrhal inflammations, in which the cells rapidly proliferate and change into mucus. Inasmuch as this mucus has been found to be bactericidal, it would seem as if the proliferation and degeneration in this case favored destruction of micro-organisms.

When the acute changes of inflammation subside, leaving perhaps a defect, as when an ulcer or abscess forms, then the development of formative cells from existing cells occurs for regenerative purposes. But frequently the proliferation in inflammation exceeds in degree and extent and occurs too early to be regarded as purely subservient to repair. Various factors are supposed to initiate this inflammatory proliferation by exercising a more or less direct "formative stimulus" on the fixed cells, especially

those of mesoblastic origin. This is shown by the occurrence of karyokinetic figures in the fixed cells very early after the introduction, for instance, of tubercle bacilli into the tissues (Baumgarten), although it is not established that this is invariably the first result of the action of the bacilli. In experimental inflammations of various kinds, in the cornea and in serous membranes, evidences of enlargement and of multiplication of the fixed cells also appear (Leber, Ranvier). Changes in the physical and chemical properties of the cells and the intercellular substance may induce cell multiplication. The bathing of the cells in a richly nutritive exudate and the presence of numerous leukocytes are conditions that may be regarded as favorable to cell growth.

In typhoid fever a marked proliferation occurs in the endothelial cells of the lymph-follicles of the intestine, mesenteric lymph-nodes, and spleen; and the new cells acquire marked phagocytic properties, as shown by their taking up other cells (Mallory); this is seen also in other diseases.

The young tissue that develops in inflammatory proliferations, such as the so-called infectious granulomatous processes (tuberculosis, syphilis, etc.), and also in the latter stages of acute inflammations, as in the healing of a suppurating wound, is commonly known as granulation-tissue.

When such tissue is examined microscopically various forms of cells are seen:

1. Small round cells, with deeply stained, irregular, lobulated, and horseshoe-shaped nuclei—polymorphonuclear leukocytes—which take no active part in the formation of new tissue; many are apparently consumed by the formative cells.

2. Cells of variable size, with round or oval, rather faintly staining nuclei and oval, spindle-shaped or branching bodies—formative cells derived from pre-existing cells.

3. Multinuclear giant cells; these occur in granulation-tissue of bacterial origin, such as tuberculous proliferations; also in wounds, around necrotic material, and about foreign bodies. Their origin is variously interpreted: from the confluence of leukocytes (J. Arnold, Ziegler, Metschnikoff), or from that of epithelial and formative cells; from fibroblasts by multipolar or multiple mitosis, or nuclear fragmentation without division of the body (Virchow, Weigert); from endothelial cells, etc. The tendency is to regard giant cells in infectious processes as phagocytes; when developed in the vicinity of foreign bodies of various kinds their function is clearly one of absorption and removal. When their function is fulfilled multinuclear giant cells may split up into small cells.

4. Among the various cells are also found some that cannot be distinguished morphologically or otherwise from large mononuclear hyaline leukocytes. While the researches of Ziegler, Nikiforoff, Marchand, and many others have led to the general opinion that the leukocytes cannot form fixed cells, uncertainty still obtains as regards the large hyaline variety. The cell is not distinguishable from fibroblasts in one stage of their growth. Metschnikoff attributes to this cell the power to change into connective-tissue cell. He claims that in the tadpole and other lower animals the development of leukocytes into fixed cells can readily be traced; and he and his pupils lay more stress on the part taken by leukocytes in the inflammatory tissue formation than others who have studied this problem. J. Arnold injected into the circulation small foreign bodies, around which the leuko-

cytes formed a wall; later the bodies became attached to the wall of the vessels and enclosed in a capsule of connective tissue formed by cells the origin of which he is inclined to trace to the large mononuclear leukocytes. However, the question whether the large hyaline leukocytes can become fibroblasts must still be considered open.

5. Small lymphocytes and plasma-cells. In practically all cell accumulations of inflammatory origin cells occur with dense, round, deeply staining nuclei and a small rim of protoplasm—the small lymphocytes. Unna has shown that many inflammatory infiltrations contain in varying numbers a peculiar cell, the protoplasm of which stains blue with methylene-blue, while the nucleus, usually eccentric in its situation, stains more lightly and appears as a clear spot with a few irregular chromatin masses scattered along the nuclear membrane and in the interior. This is the *plasma-cell*. Its shape varies under different conditions; it may be pear-shaped, oval, or elongated. In suitable preparations the shape, the somewhat granular or broken-up cytoplasm, and the characteristic nucleus render this interesting cell easily recognizable even in sections stained with hematoxylin, which gives the cytoplasm a faint bluish tinge. Most writers (von Marschalko, Councilman, etc.) believe that the plasma-cell originates from locally pre-existing or emigrated lymphocytes. Others consider them emigrated large mononuclear leukocytes, the protoplasm of which has undergone nutritive changes, causing it to be basophile. Mitotic figures indicate that plasma-cells may multiply (Councilman). Many so-called round-cell infiltrations are made up largely of plasma-cells. The special significance of the plasma-cell has not yet been discovered; the cell is not phagocytic. There is also division of opinion as to its fate; Krompecher and others claim that it can form mature connective tissue, but this is by no means definitely established. Its occurrence in normal lymphatic glands and in the spleen has been noted.¹

Another peculiar cell of unknown origin and significance is the “mast-cell” (*Mastzelle*), also found in the outskirts of inflammatory areas and elsewhere, though in small numbers. It is characterized by the presence in the protoplasm of numerous small basophile granules, which stain red with methylene-blue; such granules are said to be metachromatic.

THE LOCAL AND GENERAL SYMPTOMS OF INFLAMMATION.

The external manifestations of acute inflammation are commonly redness, swelling, heat, and pain (rubor, tumor, calor, dolor). These are the so-called Galenic signs of acute inflammation, and the primitive definition of the process included only those states in which these cardinal symptoms are present. But inflammation may exist without any of these gross signs, so greatly has the significance of the term inflammation changed since its introduction by Celsus. To the four original cardinal signs mentioned has been added a fifth, the loss or disturbance of function (*functio læsa*); this symptom may be said to be constant.

The redness of inflammation is due to arterial, and especially to venous and capillary, hyperemia. The swelling depends upon several factors—namely, hyperemia, exudation of serum, emigration of leukocytes, and, if the process has existed for a little time, upon the production of new tissue. The pain is ascribed to the tension and the pressure upon the nerves as well

¹ For literature on the plasma-cell, see *Progressive Medicine*, p. 247, March, 1899.

as to the direct changes in the nerve-filaments ; it is subject to much variation, being generally acute where the tissue is subjected to great tension.

The temperature of the inflamed area in superficial regions may be raised above normal, but it never exceeds the temperature of the interior of the body. The higher temperature is due to the increased amount of blood that passes through the area, in consequence of which more heat is brought to the surface (John Hunter). In inflammation of the internal organs the rise of the temperature above normal is immaterial as compared with the temperature of normal internal organs taken at the same time. The fever that often accompanies inflammation has nothing to do with any local increase in heat-production. When stasis or extensive necrosis occurs in inflamed areas the local temperature may fall (Cohnheim).

The loss or disturbance of function consequent upon inflammation depends on the change in the structure and in the chemico-physical conditions of the tissue involved ; and the degree and danger of the resulting functional interference will depend on the kind and the extent of the inflammation, upon the physiologic importance of the inflamed tissue, and upon a number of local conditions that are best understood from the descriptions of inflammations in the special organs given in subsequent chapters.

The consideration of the general symptoms that develop in the course of many inflammations does not belong here. Inflammation is a purely local process. The term does not include the changes in the organism at large, the fever, the general intoxication and infection, directly or indirectly associated with many forms of inflammation. Local inflammation may be accompanied by severe constitutional symptoms and changes due to the absorption by the blood and the lymph of the toxic products of pathogenic micro-organisms and of disintegrating tissue and exudate. Bacteria and tissue-fragments may enter the general circulation, and, lodging in internal organs as emboli, give rise to secondary or metastatic processes. These important problems, as well as the changes that occur in the blood at large in various inflammations, are discussed elsewhere.

THE FORMS OF INFLAMMATION.

Inflammation appears in various forms, depending on the tissue involved, the nature and intensity of action of the inflammatory agent, and upon other conditions. An etiologic classification, which would be the most desirable, is hardly possible, because the same agent may give rise to different forms of inflammation and different agents to the same forms. A classification depending on the anatomic nature of the changes and of the exudate also meets with difficulties, because the inflammatory process presents manifold peculiarities and variations according to the structure, function, and position of the tissue it involves.

Inflammations may be grouped in a general way according to the nature of essential causes : traumatic, thermal, chemical or toxic, and infectious.

Traumatism produces inflammation in various ways. The mechanic trauma as such may cause passive alterations in the vascular wall and disturbances of the vasomotor innervation favoring exudation and the emigration of leukocytes, which are attracted by the chemical products that arise from dead cells and from extravasated blood in the tissue-spaces. Undoubtedly the most important role played by trauma as an inflammatory agent consists

in causing breaks in the coverings of the mucous and cutaneous surfaces through which micro-organisms gain entrance.

Thermal influences—heat and cold—cause inflammation by direct changes in the tissues when their action is of moderate intensity and transitory or brief duration. More prolonged action results in diffuse necrosis, followed by reactive inflammatory phenomena around the dead tissue, absorption, and repair.

Chemical substances—as mineral acids, alkalies, many salts, etc.—cause, when acting in great concentration, complete and instantaneous necrosis of the tissues, so that inflammation appears only at the margins of the necrotic tissue. There are also chemical substances the action of which is more selective. Here belong the substances that attract leukocytes, so as to cause suppuration, and also many dilute acids, alkalies, and salts, cantharides, etc., which may produce inflammatory lesions at the point of primary contact as well as at the point of elimination, *e. g.*, the intestinal mucous membrane and the kidneys. Toxic substances may arise in the interior of the body in consequence of abnormal metabolism, and cause acute and chronic inflammations, as in gout and uremia (uremic pericarditis). Many forms of dermatitis are now regarded as due to auto-intoxication of this kind.

The infections are the most important causes of inflammation. The reactive tissue-changes in consequence of bacterial lesions assume many forms, but they are characterized especially by a more or less well-marked progressive tendency depending upon the production of new generations of bacteria and new doses of toxic substances. Bacteria may cause inflammation in the skin and elsewhere, due to direct infection from without; or they may be carried by the lymph and blood and cause inflammation in the internal organs. The toxic substances produced in local bacterial inflammations are often absorbed by the blood, and cause general toxic symptoms and inflammatory changes at the place of elimination and elsewhere. On this account and because of their progressive tendency the infections give rise to the most important inflammations from a practical standpoint; they are also the most frequent.

The classification of the infectious inflammations in a simple manner is not possible except in the most general way. The form of the inflammation caused by a given organism is not constant. The modifying influence of the relation between the resisting power of the cell and the virulence of the micro-organisms may be recognized in all infectious inflammations. Attenuated anthrax bacilli in a susceptible animal or virulent bacilli in a refractory animal may lead to local suppuration; while virulent bacilli in a susceptible animal causes rapid serous exudation without leukocytic accumulation, and a general septicemia. Tubercle bacilli may give rise to a variety of forms of tuberculous inflammation. Under varying conditions the same micro-organism may cause various forms of inflammation that merge insensibly one into the other, and which are described in detail in the sections dealing with the pathologic anatomy of the organs.

Anatomically the various forms of inflammation depend on the character of the exudate, the amount of the leukocytic emigration, and the extent and nature of the changes in the fixed tissues. As already indicated, these anatomic forms are far from being etiologic entities.

According to the character of the exudate, inflammations are divided

into *serous*, *fibrinous*, *hemorrhagic*, and *purulent*, with combination forms, as *serofibrinous*, *fibrinohemorrhagic*, *seropurulent*, etc. The manner of formation of the inflammatory exudates has been discussed. The exudation may form in the tissue-spaces, the lymph-vessels, and on the surface of serous and mucous membranes. If the serous exudate accumulates in the spaces of a tissue, the condition sometimes is called inflammatory edema. Inflammations of mucous membranes accompanied by serous exudation, the formation of much mucus, and desquamation of epithelial cells are called serous catarrh, seromucous catarrh, and desquamative catarrh; when mucus predominates the inflammation is designated catarrhal.

Inflammations of mucous membranes accompanied by the formation of fibrinous exudates are frequently called **croupous**. The fibrinous layer usually forms where the epithelial lining has been destroyed, so that the connective tissue is exposed; from such places the membrane may spread over the epithelium, as yet intact. In the familiar disease, croupous, fibrinous, or lobar pneumonia, which is caused by the *Micrococcus lanceo-*

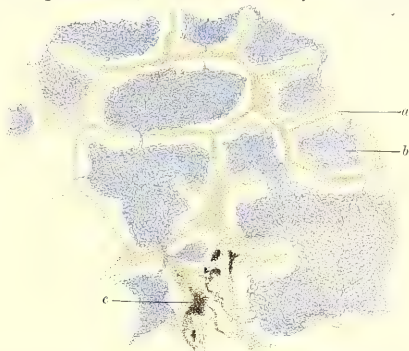


FIG. 50.—Fibrinous inflammation of lung: a, wall of alveolus; b, alveolus filled with fibrinous exudate; c, coal-pigment. Weigert's fibrin stain. $\times 125$.

latus, there is formed in the alveoli a network of threads of fibrin enclosing in the meshes various kinds of cells (Fig. 50). Upon mucous membranes, such as the pharyngeal or laryngeal, fibrinous inflammations form removable membranes, and are usually caused by the diphtheria bacillus. The vapors of strong chemicals, like ammonia, also induce fibrinous inflammations.

Suppurative inflammations and the resulting abscesses and ulcers are generally caused by the so-called pyogenic or pus-micro-organisms. The number of bacteria that may produce positive chemotactic substances, so as to lead to pus formation, is very large. In addition to *Staphylococcus* and *Streptococcus pyogenes* and other less common pyogenic micro-organisms, it has been shown that the gonococcus, typhoid bacillus, *Bacterium coli commune*, *Micrococcus lanceolatus*, *Bacillus mucosus capsulatus*, *Micrococcus tetragenus*, *Bacillus proteus*, ray-fungi, and others may lead to suppuration. Chemical suppuration independently of bacteria is now a well-established fact. This form has only a limited clinical interest; it heals readily, does not tend to spread or to cause metastatic abscesses; the cause does not

reproduce itself. Among chemical, positively chemotactic substances the following are capable of producing pus: mercury, turpentine, petroleum, dilute croton oil, 5 per cent. to 10 per cent. solutions of silver nitrate, calomel, creolin, digitonin, digitoxin, and the oils of cajuput, cloves, juniper, mustard, savin, etc. (Councilman, Uskoff, Steinhaus, Janowski, Leber, and others).

The development of suppurative inflammation may be studied well in the so-called miliary abscess due to implantation upon the walls of capillaries of micro-organisms carried as emboli in the blood-current. The bacteria, or rather the toxic substances produced, first cause necrosis or necrobiosis of the cells with which they come in contact, shown microscopically by the absence of the nuclei and the indistinctness of the outlines of the cells around the microbial colony. Soon vascular changes occur with leukocytic emigration (Fig. 51); the leukocytes are attracted toward the toxic substances, and form a zone around the dead cells and the bacteria. Here they are directly exposed to the poisons produced by the latter, and those that have moved nearest the center of microbial activity and perhaps

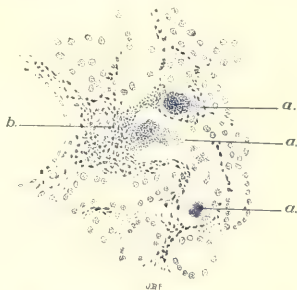


FIG. 51.—Acute ascending nephritis, secondary to cystitis, and caused by *Staphylococcus aureus*: *a*, micrococcal colonies in uriniferous tubules; the epithelium of which is necrotic; *b*, polymorphonuclear leukocytes accumulating about the microbes. Hematoxylin and eosin. $\times 125$.

incorporated bacteria are soon killed. The emigration continues and the central destruction extends. The ferments produced by the bacteria and by the cells liquefy the dead tissue; the exudation from the vessels does not coagulate, and there is produced a turbid, grayish liquid, or pus, which contains leukocytes—pus-cells or pus-corpuscles—in large numbers. The resulting cavity, or abscess, which was at first microscopic in size, may extend in the manner indicated, or coalescence of several abscesses may give rise to large cavities.

Suppurative inflammation in any tissue, due to direct infection from without or from the blood or lymph, begins essentially in this manner. When the pus becomes a little older the cells undergo albuminous and fatty changes and necrosis, and the fluid assumes a yellow, cream-like color. In the meantime the fixed cells around the focus proliferate, and a layer of formative tissue is produced, which becomes infiltrated with leukocytes. The inner layers of this wall undergo gradual disintegration, while on the outside new tissue is constantly being formed from the old, so that finally a distinct wall or capsule is produced.

During the development of such changes in the skin or subcutaneous tissue there is excellent opportunity to study the cardinal signs of inflammation—the redness, swelling, heat, and pain.

The further fate of an abscess varies. The pus may putrefy, due to a mixed or secondary infection with saprophytic bacteria. The cavity may be opened by the surgeon or it may open spontaneously; the process extends diffusely if the contents flow out on a serous membrane or into loose tissues; or the micro-organisms may die, the contents becoming sterile. More or less complete absorption may follow, with cicatrization and perhaps calcification.

When the pus micro-organisms are relatively virulent the suppurative inflammation may assume a spreading or diffuse form, giving rise to indistinctly circumscribed purulent infiltrations (called phlegmons) or to diffuse suppurative exudates on serous membranes. In mucous membranes suppurative inflammation may remain superficial, causing mucopurulent exudates, epithelial desquamation, and necrosis.

Diphtheric inflammation is characterized by coagulation necrosis of the inflamed tissue, which with the plasmatic exudate forms an adherent fibrinous layer (Fig. 52). The terms diphtheric inflammation and diphtheria are not synonymous. Diphtheria is caused only by the diphtheria bacillus,

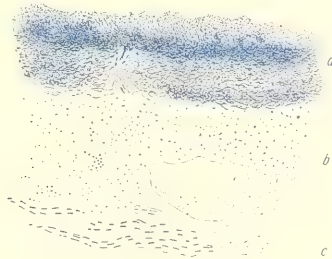


FIG. 52.—Diphtheric esophagitis, due to the diphtheria bacillus: *a*, mucous membrane which has undergone coagulation necrosis and formed a fibrinous network; *b*, swollen and infiltrated submucous coat; *c*, muscular coat. $\times 125$.

while diphtheric inflammations, unfortunately so called, may be caused by a number of other micro-organisms than the diphtheria bacillus, and also by chemical and thermal agents.

It would be much better to confine the terms diphtheric and diphtheria exclusively to the changes produced by the diphtheria bacillus.

This form of inflammation occurs especially on the mucous membranes of the pharynx, intestines, urinary bladder, and the vagina, as well as on the skin. The necrosis may involve only the superficial layers of the epithelial covering, the cells of which lose their nuclei and are changed into irregular flakes; or it may involve the subepithelial connective tissue as well, the dead tissue together with the exudate being converted into a granular, hyaline, or fibrinous layer, quite firmly attached to the underlying structures; if it is torn away, it leaves a ragged surface. The necrotic and coagulated material presents a whitish, grayish-white, or yellowish appear-

ance, which in the intestine may become green or brown from staining with bile and intestinal contents. Later the deeper layers may soften, the membrane after its detachment leaving a distinct loss of substance.

Productive inflammation is characterized by the formation of new tissue. The term is applied to forms of inflammation in which the production of new tissue seems to stand in direct relation to the inflammatory agent, and to cases in which the new tissue appears to be produced for the purposes of regeneration or replacement of old tissue. Distinction between purely regenerative proliferation and proliferation due to direct stimulus of the inflammatory agent cannot always be carried out. Generally speaking, the new tissue formed in productive inflammations is connective tissue, which presents itself in the early stages of its existence as formative tissue, or granulation-tissue, subsequently undergoing either various kinds of degeneration, or changing into mature, fibrillated connective tissue with the tendency to shrink and contract (cicatricial tissue). A distinct group of productive inflammations is that caused by certain micro-organisms which produce progressive formations of granulation-tissue with a more or less well-marked tendency to necrosis. It includes the productive inflammatory changes in various tissues produced by the specific micro-organisms of tuberculosis, syphilis, glanders, rhinoscleroma, and actinomycosis, and certain blastomycetic and protozoan processes in the skin and elsewhere. In this group of inflammations, the *infective granulomas*, the inflammatory exudation and leukocytic emigration are usually not so well marked or of late occurrence; but it is not to be forgotten that the bacillus of tuberculosis, for instance, may cause acute exudative inflammations. In mucous membranes productive inflammatory changes may lead to a general hyperplasia of all the structures in the mucosa, while in other cases the overgrowth may involve only some of its constituents, as, for instance, the lymph-nodes in the nasopharyngeal and intestinal mucous membranes. Productive inflammation following mere physical irritants is observed in the lungs in the chronic proliferation of the connective tissue that follows the inhalation of coal-dust and fine silicious particles. Condylomas and warts in the skin, osteophytes, and hyperostosis of bones are additional instances of purely inflammatory proliferations arising in various conditions, and due apparently to direct stimulation of the cells or caused by increased nourishment on account of the hyperemia and the exudation. Another important group of chronic productive inflammations is that characterized by a degenerative atrophy of the specific cells and hyperplasia of the connective-tissue stroma of organs like the liver, the kidney, the stomach, etc.—the so-called *chronic interstitial inflammations* (cirrhosis of the liver, chronic interstitial nephritis). The essential changes are degeneration and necrobiosis of the glandular cells, leukocytic infiltration and proliferation of the connective tissue, with the obliteration of old and the formation of new vessels, and usually contraction of the new tissue, leading to induration and shrinking of the organs. The question whether the degenerative changes in the parenchymatous cells are primary and the growth of connective tissue consecutive, or whether the connective-tissue hyperplasia is primary and the parenchymatous degeneration secondary and due to the increasing contraction of the new-formed fibrous tissue, cannot be said to have as yet received definite answer. It is probable that either process may be the starting-point. Of late, however, and more especially since the importance of chronic intoxications and auto-

intoxications has become more fully recognized, the opinion has grown stronger that many such diffuse productive inflammations are due to primary parenchymatous degenerations and necrosis, consecutive to which the tissue of the stroma undergoes hyperplasia (Weigert, Ackermann, and others). Flexner has demonstrated the development of chronic interstitial changes in the liver secondary to degeneration and necrosis produced by the experimental introduction of toxic substances.

In connection with necrosis, infarcts, degenerations, and thrombosis it was stated that new connective tissue may in time replace the necrotic, atrophic, and useless material. Inasmuch as inflammatory exudation and leukocytic emigration are occasionally observed around such areas during this process, it is also warranted to regard such replacement fibrosis (Adami) as of inflammatory origin, as a species of productive inflammation intended to repair injury and remove useless and noxious material.

THE TERMINATION OF INFLAMMATION; RESORPTION; THE HEALING OF DEFECTS AND OF ASEPTIC AND SUPPURATING WOUNDS.

The individual inflammations present many variations as regards course and termination, depending upon the special cause and upon local and general conditions of the organism. The reparative and counteracting tendencies of the inflammatory process proper are far from being wholly and immediately victorious. Necrosis, suppuration, the accumulation of exudate, are results which, as the causes of inflammation subside, lead to resorption and repair. Productive inflammations with the development of cicatricial tissue lead to contraction and induration which seriously interfere with functional activity.

Acute inflammatory reaction due to influences of brief duration and only moderate intensity are often followed by rapid restitution; but a prolonged bacterial infection associated with necrosis, severe vascular changes, and much exudation requires a long time for definite repair. The removal of the exudate, of the necrotic material, as well as of foreign bodies, is accomplished by means of lymphatic and venous absorption, aided by digestion and by phagocytosis on the part of leukocytes, formative cells, and giant cells. A mild degree of chronic inflammation persists around many necrotic masses and exudates until their complete removal is accomplished. Serous exudates are quite rapidly absorbed by the lymphatics and veins. Fibrinous exudates as well as pus require a longer time; the fibrin must first be redissolved; in many inflammations of this kind, especially when some form of obstruction, such as pressure or thrombosis, delays venous and lymphatic absorption, the exudate may become inspissated, infiltrated with lime salts, and closely surrounded by new fibrous tissue. Emigrated leukocytes that have remained active may, during resorption, immigrate into the lymph-vessels or aid actively in the removal of the dead material. Necrotic tissue situated superficially is loosened by digestion and phagocytosis from the healthy and allowed to drop off (sequestration, demarcating inflammation); solid necrotic masses in the interior are gradually absorbed and replaced with living tissue or encapsulated, undergoing later perhaps calcification or softening. As already stated, necrotic tissue and exudate may attract leukocytes and embryonal cells, which take up in their interior bacteria, pigment-granules (pigment-carrier cells), remnants of cells and tissues that

have undergone necrosis and fatty as well as other changes (granule-cells); these substances may be dissolved by intracellular action or carried to the regional lymph-nodes or the internal depots for the removal of useless materials. Some of the leukocytes are taken up by formative cells, which in this manner receive food. Necrotic masses as well as foreign bodies may become surrounded by granulation-tissue in which lie multinucleated giant cells that assist actively in the removal of the foreign material, on the surface of which they produce small depressions. The regeneration of the dead cells is accomplished according to the principles of regeneration in general; extensive necrosis, the death of highly specialized cells, such as ganglion-cells, and infected wounds are not followed by perfect regeneration, but by an inferior species of repair, namely, cicatrization. Cicatricial or scar-tissue is granulation-tissue or formative tissue that has changed into a finely fibrillated tissue with few vessels and few small cells.

Many exudative inflammations of serous membranes terminate in the growth of new fibrous tissue that leads to permanent adhesions of apposed surfaces or to localized fibrous thickenings. This new growth follows destruction of the endothelial cells and of the subendothelial connective tissue. Granulation-tissue forms about necrotic masses, abscess-cavities, and foreign bodies; as absorption takes place it substitutes the material removed and changes into a scar, or it forms a fibrous capsule around the calcified or softened detritus that remains unabsorbed.

Healing of Aseptic and Suppurating Wounds.—The underlying factors are the same in the healing of all wounds and defects, inasmuch as new tissue is always necessary even when the margins of an aseptic incised wound are held in perfect apposition. Healing of aseptic incised wounds which is accompanied with a minimum and, to the surgeon, invisible amount of granulation-tissue, is known as healing by primary union or first intention.

The best conditions for primary union are obtained when the margins of the wound are least injured, when infectious and toxic influences are reduced to a minimum, and when perfect apposition is secured. The primary injury—the incision—leads to some bleeding and to the oozing from the tissue-spaces of a little serum, which coagulates into a fibrinous layer, gluing the margins together. Then follows a mild inflammation in the margins of the wound. The exposure to the air, the solutions employed in dressing the wound, the substances in the extravasated blood, the dead or maimed cells, all combine to produce substances that attract leukocytes. Moreover, a mild infection cannot always be excluded, even in a clinically aseptic wound. The vessels dilate and a little serous exudation occurs. These changes favor healing; the leukocytes remove dead material, while the serum and the leukocytes increase the nourishment of the formative cells. In the meantime the fixed cells divide, formative cells lie in the tissue-spaces on each side of the wound as well as between the margins; new capillaries may form; the fibroblasts secrete a homogeneous or fibrillated intercellular substance that definitely holds the margins together, while the surface becomes covered with new epithelial cells. The final result is a small strip of connective tissue which with time becomes almost indistinguishable from the surrounding tissue. In favorable cases the papillary layer of the skin is almost wholly reproduced, so that the site of the wound may become nearly invis-

ible ; otherwise the wound is marked by a flat, smooth line, at first red, but subsequently whitish.

The healing of open wounds is accomplished with visible granulation-tissue, and is called healing by secondary union or by second intention. This form of healing may occur with or without infection. In an open, non-infected wound the course of healing may be outlined as follows : After twenty-four hours the margins and the floor are red and swollen ; a few shreds are seen, and there is a slight amount of grayish exudate present ; on the second day the individual tissues are no longer recognizable ; the tissue is soft and grayish red, and a reddish-yellow fluid covers the surface ; the margins of the wound and the tissue immediately adjacent are red ; the exudate contains many leukocytes. A mild inflammation of the floor and margins exists. But already on the third or fourth day small red nodules are visible beneath the exudate, which soon coalesce and form a red, granular surface—"the granulation-surface"—due to the formation of new vessels and of embryonal tissue. Leukocytes are especially numerous in the upper strata of this tissue. Afanassieff has shown that the serum in granulation-tissue is markedly bactericidal, and that virulent anthrax bacilli placed on healthy granulating wounds are destroyed, and do not produce a general infection, so that granulation-tissue forms a protective layer against microbial invasion.

The fibroblasts and capillaries proliferate until the defect is filled ; intercellular substance is produced ; the walls of the new capillaries become thicker ; the hyperemia ceases as the wound is covered with new epithelium derived from the cells at the margin. As the granulation-tissue is transformed into scar-tissue many of the new vessels are closed ; others contract their lumen, so that the vascularity diminishes. The subsequent shrinking of the cicatricial tissue may lead to serious distortions in the case of large defects healed in this way.

Practically a similar process takes place in the healing of suppurating wounds ; here the course may be greatly delayed and disturbed by the continuous death of the surface of the granulation-tissue on account of the action of the micro-organisms ; or there may occur a more luxuriant and erratic development of embryonal tissue without leading to the formation of scar-tissue. Luxuriant and persistent growth of granulation-tissue is frequently observed when foreign bodies, such as pieces of cloth or sutures, lie at the bottom of the wound, or when suppuration, and especially when tuberculosis, is present. Otherwise the growth of new tissue ceases when the defect is closed, according to the general law governing the processes of regeneration, that the amount of tissue to be produced is determined by the functional necessities in each case. When the development of granulation-tissue (and the resulting fibrous tissue) for unknown reasons passes beyond normal bounds and pays no heed to physiologic laws of growth, large masses of scar-tissue may result, that are known as keloids.

CONCLUSION.

The definitions and theories advanced from time to time in explanation of inflammation are very numerous and often contradictory. In recent years it has become more and more evident that the only theory that allows the full meaning of inflammation to be grasped is the broad, biologic conception which recognizes in inflammation an adaptive, protective, and repar-

ative tendency common to the reactions to injury among all animals. It is in a large measure to Metschnikoff that pathology owes this broad conception concerning the significance of the natural phenomena of inflammation. It is probably not practicable to frame a concise definition of inflammation in which the exact part played by each factor can be fully indicated. The definition must be general; the moment phagocytosis or any other single phenomenon is emphasized to the exclusion of others, the notion of inflammation, its meaning and tendency, is liable to become one-sided and obscure.

It has been pointed out in the preceding pages that inflammation brings into operation a number of factors to counteract harmful agents, protect the organism at large, and effect healing. The common mode of origin, the similarity of the changes (though combined in differing proportions), and the evident tendency of the inflammatory processes to protect and repair, justify fully the teaching that inflammation is essentially an adaptive, protective, and reparative process, a means of self-preservation. Yet it must not be forgotten that the mechanism of defence and preservation is far from perfect; the exudate may possess but little bactericidal power; the phagocytes may be powerless, or the bacteria may multiply freely within them, as in tuberculosis; extensive destruction of tissue may occur before the virulence of the bacteria is neutralized; general infection and intoxication may cause death; the fixed cells may form imperfect material for repair or multiply in excess; the resulting cicatricial tissue may lead to serious functional disturbances. The inflammatory reaction does not respect the relative importance of the tissues: thus, violent inflammatory exudation may cause occlusion of the larynx, or, in the meninges, cerebral compression, and the fibrous tissue produced in repair after endocardial infection may produce valvular disease. These disastrous consequences cannot always be regarded as unavoidable in order that inflammation may fulfil its primary purpose. Hence inflammation, though biologically an adaptive and preservative process, may appear harmful to the physician, requiring the intervention of medical art. Taking all things into consideration, we may conclude that inflammation is a reaction to local injuries, calling forth protective and reparative measures; but that it is an imperfect pathologic adaptation, often leading to consequences that are dangerous *per se* and defeat its purpose.

TUMORS.

Introduction.—Modern ideas concerning the pathology of tumors may be said to have begun with the publication of Virchow's *Die krankhaften Geschwülste* in 1863. At this time, with the basis furnished by the cell doctrine, the knowledge of tumors was rescued from the chaos into which previous speculation had brought it. Since the time of Virchow's classic production a vast amount of information upon tumors in their various aspects has been recorded, and to this fund of knowledge each passing year makes its contribution. Paradoxical as it may seem, however, our increasing knowledge has in certain directions only served to make more confusion, and in one particular direction, viz., as regards the *cause* of tumors in general, speculation is as rife and almost as fruitless as it was before the modern era. Etiology is the only certain guide to perfect conceptions of pathologic processes, and with etiology obscure, as is the case with the true tumors, we grope in the dark when attempting to solve many of the problems presented in their life phenomena.

Definition.—Without a clear conception of all the factors which lie at the beginning of tumor formation, it is not possible sharply to define them. How difficult the matter of definition is can be best illustrated by noting the fact that almost every prominent authority upon tumors has given a definition differing from that of others working in the same direction. With so many aspects as the study of tumors presents, each author has attempted to define from the particular phase of the subject into which his individual studies have taken him. When it can be said of this or that variety of tumors that it is due to such and such a cause, as we say of tuberculosis that it is the disease consequent upon the invasion of the tubercle bacillus, definition will define. Until then no single definition can cover the ground.

In the larger and more common forms, tumors are familiar objects to all as localized swellings in various portions of the human body. Not every localized swelling is a tumor, however, and the veriest tyro in medicine would have no hesitation in separating the reddened or fluctuating swelling of an acute abscess, or the mass of overdeveloped muscle on a blacksmith's arm, from a cancer of the breast. But all tumors are not large; many are almost or quite microscopic in size. Neither are all tumors localized swellings, for they may grow very diffusely. Further, while the differentiation of an acute abscess and a well-marked tumor is not difficult, there are firm, localized swellings arising from pyogenic, tuberculous, syphilitic, and other infections that partake of many of the characteristics of true tumors.

The aim of definitions is particularly the discrimination of true tumors, or neoplasms, from such formations as result from hypertrophy or hyperplasia, from the infective granulomas, and from other peculiar pathologic deposits or growths. How difficult the task really is can be best appreciated by a survey of the voluminous controversial literature bearing upon this topic.

A definition, however, even though imperfect, furnishes a center about which our ideas may crystallize, and such a definition is acutely demanded for tumors.

All true tumors are new growths of tissue, the elements of which pre-exist in the body. They are independent new growths, or, as Thoma has happily styled them, "autonomous" new growths. Their characteristics, as now understood, are most clearly set forth by Lubarsch, whose *résumé*¹ upon the subject of these neoplasms is the most recent and comprehensive now available, and his propositions may be provisionally accepted. They are as follows :

1. In the present state of science, autonomous new growths may be defined as growths that arise often without demonstrable cause and conform more or less to the structure of the mother-tissue, but which with regard to form are atypical, and functionally either differ qualitatively from normal tissues or by reason of their anatomic structures have a function of no value to the body.

2. The classification of these new growths is best based on histogenetic and physiologic principles.

3. It is at present impossible to give a single comprehensive explanation for the formation of these tumors.

Classification.—The imperfect state of our information concerning the ultimate causes of the various forms of tumors makes the matter of classification difficult ; and while numerous systems have been proposed, the test of increasing knowledge has shown weak points in them all. Since tumors spring from the elements of organs and tissues of the body, it is to be expected that they will retain more or less perfectly a morphologic affinity with the parent-tissue. This is the case with many kinds of neoplasms, and in consequence a basis for classification is furnished which, if not perfect, at least serves for descriptive purposes. It is this histogenetic basis that Lubarsch refers to in his second proposition ; and since Virchow's classic publication upon tumors it has been more or less liberally applied. Certain kinds of tumors, as we shall learn, do not retain the impress of their parentage, and such tumors are separately considered upon the basis of their peculiar physiologic characters. The terminology of most tumors, as at present adopted, is essentially a morphologic one, founded upon our notions of the histogenesis of tumors. Thus, a tumor composed of muscle-elements is a myoma ; one composed of neuroglial elements a glioma or neuroglioma ; and so on, as will be seen when the separate varieties of tumors are discussed. Two great varieties of new growths with special life phenomena are represented by the sarcomas and the carcinomas. It must not be forgotten, however, that the present classification and terminology are largely artificial ; and that insensible gradations occur which unite the varieties of tumors so as to leave no definite line of separation.

MORPHOLOGY OF TUMORS IN GENERAL.

Anatomic Features.—The variations of neoplasms in *size* is a well-known characteristic. A tumor may be so small as to be only visible to the eye ; indeed, the nodule may even be so minute as to be detected only by the most careful microscopic examination. Again, it may reach

¹ *Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie*, ii., 1895, 1897.

an enormous size, as seen in ovarian tumors, which may become larger and heavier than the body in which they originate.

There is no constancy in the *shape* assumed by tumors, although there is a general tendency for these formations to take a spheric form. All gradations from more or less spheric to flat masses may be encountered. The shape of the tumor-mass is often influenced by its surroundings, those growths springing from free surfaces tending to extend symmetrically, producing rounded forms, while those which are confined often assume the configuration of the cavity in which they lie. A whole organ may become filled with a new tumor-growth, while other growths spontaneously take an organoid form, so that it sometimes becomes possible to detect a distinct resemblance between a tumor and one of the viscera. When we learn that all tumors are composed of cellular units, subject to many of the laws governing the development and multiplication of cells in general, it is evident that this subject of shape as relates to lines of growth becomes an important study—one in which we are unfortunately quite ignorant.

Anyone who has handled tumors must have been impressed with the different grades of *consistency*. Some are so soft and friable as to fall apart on the most cautious manipulation; while others, even those not bony in nature, attain a stony density. Even in a single growth a uniform consistency is not always reached.

Most tumors are white, or show but a shade of grayish or pinkish *color*; but varieties are found which take distinct colors, like red, yellow, green, sometimes culminating in dead black. Usually the color of a tumor differs from that of its abode, so that its presence is readily detected. In exceptional cases a neoplasm so closely simulates the color and consistency of the structure in which it lies as to be discovered with difficulty.

In *relation to surroundings*, important differences, often highly important for the host, are met. A distinct membrane or *capsule*, a superficial covering of the tumor, separates it abruptly from the organ in which it is located, so that it can be enucleated with readiness. At other times the periphery of the tumor-mass remains sharply circumscribed, even though a true capsule is absent. Unfortunately, this respect for enveloping or contiguous structures is not shown by all kinds of neoplasms, since certain of them, without capsular boundaries, encroach more or less intimately upon the adjacent tissues until, in a particular class of tumors, an unbounded invasion occurs.

Upon incision and dissection, even without microscopic aid, a great deal may be learned concerning tumors. In many of them the resemblance to familiar animal tissues is so great that no trouble is experienced in recognizing their nature. Thus the fibrous, cartilaginous, and bony tumors, the fatty and the blood-vascular tumors can at once be placed in their proper categories. The tumor-tissue is generally quite uniform and homogeneous in appearance; but to this rule there are many exceptions, for heterogeneous material of a fatty, cheesy, gelatinous, or purulent appearance is present in some tumors, along with fluid contents like blood, urine, bile, and serum. Again, it is possible to obtain from a single tumor portions of distinctly different structures, like islands of cartilage or bone in a fibrous ground-substance. Such formations are called *mixed*, in contradistinction to the *simple* tumors.

The question of *habitat* is most tersely answered by Ziegler, when he

states that "tumors may be found in any tissue possessing capability of growth."

As to the *multiplicity of tumors*, all gradations from a single example of one variety to countless numbers of new growths in the same organ or tissue, or in different organs, are observed. Sometimes a number of similar growths may arise independently; or several distinct varieties of tumors, also of independent origin, may be simultaneously encountered in the body. In one portion of the body the original or *primary tumor* may be located, and scattered from it, both near and far, other neoplasms of the same nature (*secondary tumors*) are to be found. These secondary tumors may possess considerable bulk; they may be nodular growths; again, they may be scattered in dust-like particles, permeating a whole organ as a *diffuse growth*.

Histologic Features.—The study of the minute anatomy of tumors, especially when aided by improved histologic methods, has furnished most important additions to our knowledge; and as methods are refined, more and more is learned. A rational foundation was laid for the study of these objects when it was discovered that tumors, like the organs and tissues of the body generally, were composed of *cells* the morphology of which was often like that of one of the fundamental tissue-elements. It was this morphologic identity which led to the conviction that *tumors arose from cells which were pre-existent in the body*. Many attempts to shatter this conception of the origin of tumors have been made, but it must still be held inviolate; and with this notion clearly before us it becomes an easier task to interpret both their histologic and anatomic variations.

The cells composing many of these adventitious growths not only arise from pre-existing cells, but they retain many of the morphologic peculiarities of their parentage; they should therefore tend to reproduce the structural features of their prototypes. This is essentially the case, for these cells exhibit the structure of tissue-cells, and their grouping, their intercellular substance, their vascular supply, and even their metabolic products may all recall their ancestry. Thus the details relating to the cellular morphology of many kinds of neoplasms become but a rehearsal of the characteristics of normal tissue-elements. It is sufficient here to say that we find fibrous, fatty, cartilaginous, osseous, muscular, neural, and glandular tumors, the component elements of which resemble in structure and arrangement similar cells in normal tissue. Moreover, what holds true for the cells also applies to the elements of the cell—to the cell-wall, cytoplasm, and the nucleus with its component parts. These considerations, firmly fixed, make it clear that for most tumors there exists no such thing as a *specific tumor-cell*—a cell so peculiar in its organization that from it alone one could say that it sprang, not from normal tissue, nor from tissue the seat of inflammation, of infection, of regeneration, or of hyperplasia, but from a tumor. A fundamental point in relation to the microscopic anatomy of tumors is hereby emphasized, for it is not so much by their microscopic elements that these objects are differentiated, as by the *relation of these elements to each other, and especially to their environment*.

Tumors the elements of which exhibit the morphologic stamp of mature normal tissue generally have no strikingly peculiar physiologic characteristics, and are separately considered as *benign* or *benignant* neoplasms; their growth, like their structure, is orderly, and a respect for surrounding tissues

is shown. The attainment of morphologic perfection, such as has just been described, is not the case with all morbid new growths, for several varieties of tumors appear in the human body, the cellular units of which show a more or less marked deviation from typical mature tissue. Instead of reaching this perfection, the elements stop short in their development at one or another of the stages exhibited by immature or even by embryonic tissue. One species of these tumors (sarcoma) has, in some varieties, the cells, evidently predestined to become mature mesodermic tissue (connective tissue, endothelium, etc.), perverted and permanently arrested at a stage reached only by undeveloped mesodermic cells; while in another species (carcinoma) a predestination to mature ectodermic structures (epithelium, glands, etc.) seems to have been aborted. In these, the so-called *malignant tumors*, the component cells, both in their internal structure and in their groupings, depart more or less widely from the normal tissue-types, and there is a lawlessness in structure in their growth which shows no respect for environment. Not only do these neoplasms tend to disregard local confinement: they also possess the power of *colonization in remote parts of the body*. From a solitary tumor in a given locality new growths of the same kind may appear, either in the immediate vicinity of the original focus or scattered throughout the body. This process of colonization is usually designated *metastasis*; the offspring of the original colony *metastases*; and the "malignant tumors" practically monopolize this property. The departure from the normal morphology affects the whole cell with its component parts to such an extent as to make it possible occasionally to discover the presence of the tumor by the peculiarity of its isolated cells—principally by the nucleus and by the appearance presented by the figures of nuclear division.

Besides the proper tumor-cells, arranged in various combinations, there exists a *supporting ground-substance*, or *stroma*. In those neoplasms the structure of which takes the general type of pre-existing mesodermic tissues this stroma very closely resembles the connective-tissue framework of normal tissues, and forms an integral part of the growth, serving as a pathway for blood-vessels and lymph-vessels. In ectodermic (epithelial) tumors this framework or stroma is particularly prominent, sharply defining itself from the parenchyma proper. A striking peculiarity of certain primary malignant tumors is their ability to appropriate to themselves, as stroma, the framework of the organ in which they lie, in some cases even using the walls of capillaries as supports for their cells.

In and between the tumor-cells, or scattered through the stroma, *other microscopic elements* are found in tumors. Leukocytes, especially polymorphonuclear neutrophiles and lymphocytes, are present, sometimes in enormous numbers, both in the blood-vessels, in the tissue-spaces, and even within the tumor-cells. In tumors the seat of inflammatory reaction leukocytes accumulate in foci, or large abscesses may be found. Another variety of cell, probably originally a lymphocyte of the blood, is often found in the substance of tumors or in the immediate vicinity of the new growth, making a considerable bulk of the small-cell infiltration. These cells stain deeply with methylene-blue, and are doubtless identical with the so-called "plasma-cells" of Unna. Again, especially at the growing borders of tumors, both benign and malignant, cells with granules staining specifically with the basic dyes (safranin or gentian-violet, for

instance), and probably having their origin in connective tissue, are to be seen. Ehrlich and his pupils have designated these elements "mast-cells" (Mastzellen), though their significance is not yet clear. Acidophile granular cells, representing apparently both true and pseudo-eosinophile cells, also abound at times, especially where blood-destruction is going on. Connective-tissue cells in various stages of activity appear, often forming a large bulk of the small-cell infiltration marking the advance of certain growths. The cells composing some tumors seem to functionate much as similar normal animal cells do, and the microscope reveals many of the products of their metabolism, both in the tumor-cells and in their neighborhood.

Vascular channels for blood and lymph are found in neoplasms in varying proportions and degrees of perfection, and within the vessels the usual morphologic elements of blood and lymph are present. In certain rapidly growing tumors the development of blood-vessels may be so imperfect as to amount to little more than a channel between rows of tumor-cells.

An interesting question lately revived relates to the presence and source of *elastic tissue* in tumors. Where the tumor-stroma is formed from the framework of the parent tissue, elastic tissue exists as it originally did, apparently in an unaltered qualitative and quantitative condition. Whether new elastic fibers are formed in tumors manufacturing their own stroma is not positively determined, though the application of the recently perfected methods for their specific staining seems to render highly probable the view that certain tumors, both benign and malignant, ectodermic and mesodermic, are capable of elaborating new elastic tissue during their growth.

Another profitable inquiry refers to the presence of *nerves in tumors*. Eliminating those new growths arising from the central or peripheral nervous system, and naturally including nerve-cells and nerve-fibers, what can be said about the presence of vasomotor nerves in the blood-vessels of the stroma, or of sensory nerve-fibrils in the tumor-substance? All that can be asserted is, that nerve-fibrils are sometimes present in various kinds of neoplasms; but as to whether these elements represent simply the fibers previously present in the locality occupied by the foreign growth, or whether they are developed in the tumor from rudiments left in the mother-tissue, cannot be definitely answered at this time.

GENERAL PHYSIOLOGIC FEATURES.

Tumors are actual animate objects when encountered in the sites they naturally select in the living animal body. They exhibit the same evidences of vitality that enable us to judge of the life of any living animal, organ, or tissue. They grow, and, like other living things growing, they must receive nourishment, and receiving food necessitates a process of metabolism. They are supplied with nutritive juices, mostly through blood-vessels and lymph-vessels, in which course living elements, all provided by their host. They are subject to incidental diseases like the general tissue of the body. In short, these growths of new tissue which exhibit so many morphologic resemblances to normal animal structures live under many of the same physiologic laws that govern living things generally; and, like the organs of the proper animal body, they cannot live independently of their possessor. Severed from their organic connections they die, just as an amputated

limb dies ; and there is little positive evidence that, when artificially reimplanted in the body of the host, or of another animal, they can again grow, or, if at all, but temporarily and imperfectly. With the assurance that tumors themselves and their cellular components respond to general physiologic laws, it will here be unnecessary to pass in review all the details of their life history. Rather let us turn our attention to certain features of peculiar interest—some of which might be styled the *morbid physiologic characteristics of tumor-elements*.

Morbid Physiologic Processes in Tumors.—Tumors are composed of cells, and since we know from observation that tumors grow, it follows that, like other living animal structures, they grow by division of their component cells. In tumors most closely simulating tissue-types, and generally of benign tendency, *cellular reproduction* is an orderly process, with the usual phenomena of nuclear and cellular division seen in normal animal cells. The operation of nuclear division occurs both by the method of direct and of indirect segmentation (karyokinesis). In the tumor-cells themselves karyokinesis is the most constant method of nuclear division, and, so far as our present means of observation go, this phenomenon proceeds generally in an entirely normal manner.

A general tendency, which often prompts them to grow with extraordinary rapidity, and to force their way through surrounding structures, and to break through confining cavities, which is especially the attribute of sarcoma and carcinoma, is very frequently reflected in the reproduction of their cells. The nucleus, in its division, may exhibit such departures from the normal method as to make appropriate Hanseemann's term of "pathologic mitosis." In sections of such tumors, appropriately stained, one may find cells with small shrunken nuclei, containing but little chromatin, or sometimes in the same tumor monster cells with gigantic single nuclei, rich in chromatin. The number of chromosomes may be small (hypochromatosis), or much in excess of the normal (hyperchromatosis). Karyokinesis, or mitosis, may proceed by many peculiar irregularities. A marked disproportion in the two masses of chromatin, resulting from the unequal disposition of the chromosomes, gives rise to an "asymmetric mitosis." Even more striking is the phenomenon of "pluripolar mitosis," in which, instead of two attraction-spheres with their centrosomes at the poles of the dividing cell, from three to twenty or more attraction-spheres and centrosomes may be discovered in a single cell, disposed about the large and irregular central mass of chromosomes. Not infrequently, besides these cells with pluripolar mitosis, large multinuclear cells (giant cells) are found, doubtless representing a stage in the division of the pluripolar cell. Giant cells also originate from indirect nuclear fragmentation, which reaches a high degree of development in certain malignant tumors ; and in this class of tumors karyokinesis is often replaced by direct segmentation or fragmentation. It must not be concluded, however, because these various irregularities in cellular reproduction (with the possible exception of asymmetric mitosis) are frequently found in malignant tumors, that they are peculiar to them. They certainly are pathologic occurrences ; but they may develop in other situations—*e. g.*, in segmenting ova under injurious conditions, or in mature animal tissues under the influence of certain toxic agents or other pathologic factors. Besides those processes which indicate an abnormal cytologic reproduction are others that can only be regarded as degenerate in

tendency, indicative of impending or actual death of the affected cells. The chromatin of the nucleus gathers in irregular masses, which break into fine, dust-like particles (karyoclasia). These fragments or dust-like particles of chromatin may disappear by solution (karyolysis). Within the nucleus, or in the cytoplasm, bodies of various kinds and shapes ("cell inclusions") are not infrequently found. These bodies vary widely in their nature, being composed of escaped chromatin, of included and degenerated leukocytes or red blood-cells, of cellular or nuclear material with hyaline or other similar metamorphosis. The process of *vacuolation* is also seen in tumor-cells, especially of carcinoma, and immense cells with numerous dropsical cavities have been described. These changes, and others to be described, show that tumors are subject to degenerations, often culminating in death of the affected part.

Tumors situated upon the exterior of the body not uncommonly exhibit *necrosis* or death of their superficial portions, evident in more or less extensive *ulceration*. This destructive tendency is not confined to external neoplasms alone, for those situated within the body are also subject to its ravages. In some tumors large areas become necrotic, and microscopic examination shows a *diffuse necrosis* of the cellular elements. Besides these diffuse necroses there may be a process of *focal* or *insular necrosis* affecting the whole new growth, or confined to certain portions of it. This focal necrosis of tumors has many of the histologic features of focal necrosis in general, and resembles very closely this phenomenon when resulting from the action of various toxic agents, like ricin, abrin, snake-venom, or the poisonous products of bacteria.

Along with the degenerative changes culminating in the death of tumor-cells, a marked activity of the leukocytes and endothelial cells engaged in the operation of *phagocytosis* is frequently seen. The white blood-cells and the cells from the fixed tissues (lymphadenoid organs, the perivascular lymph-sheaths, or the connective-tissue lymph-spaces) gather about the dead and dying cells, both between and within them, and proceed to take into their substance such detritus as dispersed chromatin and nuclear or cellular debris. Occasionally the leukocytes, themselves in a condition of seeming degeneration, appear in the substance of apparently healthy tumor-cells, and it is a delicate question at times to decide whether the leukocytes were feeding on the cells or the cells upon the leukocytes. As a matter of fact, it is highly probable that both processes occasionally occur. Giant cells also arise in certain tumors in response to a phagocytic impulse, notably those appearing about the cholesterol crystals resulting from peculiar retrogressive changes (*cholesterin giant cells*).

The very close resemblance between the inflammatory and degenerative changes in tumors and those seen in other tissues the seat of infection suggests the possibility of *the infection of tumors*. That such an event actually takes place in tumors is shown by the frequent presence of micro-organisms. At least three kinds of vegetable parasitic organisms have been found in tumors, viz., the schizomycetes, or bacteria; the blastomycetes, or yeast fungi; and the hyphomycetes, or moulds. The presence of parasitic protozoa has also been urged by many observers.

It was the discovery of bacteria in certain neoplasms that first led to the promulgation of the parasitic theory of their origin, although more careful study showed the fallacy of the assumption in the cases in which it was advanced. In their turn the bacterial protozoa, the blastomycetes, and the

hyphomycetes have been held responsible as causative agents, as will be noticed under the head of Etiology. Whatever view may be held as to their etiologic relations, it is certain that many of these organisms invade tumors after they are formed, just as they invade other portions of the living body; and the gateways by which they obtain access are the blood-channels and lymph-channels when from remote regions, or directly when the tumor lies contiguous to an infected area or comes in contact with the exterior of the body. In the skin and mucous membranes, which constantly harbor micro-organisms, invasion is an easy matter.

Both saprophytic and parasitic bacteria may find their way into tumors, and the effects produced by them largely depend upon their pathogenic activity. These new growths are composed of masses of living cells with various kinds of intercellular substances, much like normal tissue, and from this structural condition it is to be expected that bacteria will inflict much the same damage as in the body at large. That such is the case is proved, for instance, by the production in tumors of inflammation, of pus, and of abscesses by the pyogenic bacteria. The vast number of leukocytes attracted to certain tumors is doubtless often a reaction produced by the toxic products of a bacterial infection; and the diffuse necrosis, or the localized (focal) necrosis, especially seen in tumors situated so as to invite invasion, is in all probability frequently the outcome of micro-organismal activity. This secondary invasion of micro-organisms is not always a harmful process, for there is undoubted evidence that certain infections have the power to cause arrest or even retrogression of some neoplasms, though this much-desired outcome is generally only a temporary one. Artificial infection of tumors with living bacteria, or the introduction of their toxic products, also appears to have a similar effect.

From many of their analogies, tumors may be compared to parasites living upon and at the expense of the host. It will therefore be profitable to consider here the *general relations of tumors to the host*. Many, with slow, orderly growth, are not harmful, or are harmful merely on account of their mechanic inconvenience. These are pre-eminently the *benign tumors*. Others of this class may be injurious because they act as foreign bodies. Thus, an immense abdominal tumor may become an actual burden by its size; and benign growths in the eye, ear, the central nervous system, or at the duct of some important organ may work serious mischief, even in their natural state of innocence. The case is entirely different, however, with the *malignant tumors*, which are, from their very inception, vicious in tendency. They generally grow rapidly, and even in their primary abode are not restrained, but proceed to spread in various directions. Their cells penetrate the natural spaces or clefts in the parent organ or tissue, and may even melt away more solid obstacles, like bone, which may perchance lie in their way. When this unchecked growth takes place in an important organ it is overrun and sometimes completely destroyed, the place of its own elements being taken by the foreign mass. This process affecting a vital organ, death of the individual is the natural and inevitable consequence. In their power of metastasis, also, the malignant tumors work great damage. Through the blood-vessels and the lymphatics, or by transportation over contiguous surfaces, the cells of the parent tumor are carried, and, lodging in another locality, their capacity for multiplication unimpaired, they produce secondary growths quite like those from which they sprang. Not

uncommonly the parent neoplasm is situated in a neighborhood in which it works no great mischief; but its offspring, locating in remote and often vital organs, lead to destruction.

With their propensity to become infected with pathogenic and especially pyogenic bacteria, tumors sometimes indirectly inflict damage upon the patient. The toxic products of this pyogenic infection in the circulation produce a general toxemia, which is shown by such phenomena as fever, chills, and progressive debility. It is also highly probable that in their growth the malignant tumors sometimes elaborate toxic agents through the perverted metabolism of their cells, these products again working harm to the host. The *cachexia*, or peculiar debilitated condition of individuals afflicted with malignant tumors, doubtless originates at times from this kind of slow poisoning.

THE ETIOLOGY OF TUMORS IN GENERAL.

There never has been a time when the subject of the causation of tumors needed so cautious an approach as now. With the vast mass of literature now available upon tumors in their various aspects, it becomes a difficult task to isolate the fundamental facts, particularly for purposes of didactic presentation; and nowhere is this difficulty more keenly felt than in connection with the question of etiology. Probably in this, as in other cases, a particularly unsettled state of affairs presages the birth of something new, and perhaps we are now on the eve of another era in our knowledge of tumors. Still, this important subject cannot be ignored in a treatise of this character, and brief reference to some of the views will therefore be made.

Mechanic irritation, traumatism, and previous local infection predispose to the development of tumors, and will be treated of in connection with special neoplasms. They must be regarded only as factors, however, and further search must be made for the real causative agency.

Granting that all tumors in the human body have their inception in pre-existent cells, we still have for consideration the problem which inquires into the causes leading to their development from these tissue-elements. What agency initiates the cells in this or that locality to such unusual activity as to produce from a cell, or a group of cells, by their proliferation, the tumor-mass? Why should this proliferation differ in its results from that seen in tissue regeneration, in hyperplasia, or in the new growths resulting from certain infections?

In 1882 Cohnheim attempted to answer these questions by propounding his *embryonal theory* of the origin of tumors. In its essence, as modified by its author, Cohnheim's theory ascribes the inception of tumors to misplaced embryonic rudiments, cells or aggregations of cells, which, during the various and complicated foldings of the embryo, and the shifting of its cells, become misplaced. In the further development of the embryo these tissue-rudiments are supposed to lie dormant but alive, and at some subsequent period, either early or late in the history of the individual, they resume activity and furnish the nucleus from which, by cellular proliferation, a tumor arises. This theory, though of purely speculative origin, has much to lend it support. Indeed, for a certain class of neoplasms—those arising in the fetal period or those distinctly congenital in their origin, or

that class containing more or less perfect reproductions of various kinds of mature tissues, and even organs of the body (the *teratomas*)—Cohnheim's hypothesis seems to afford the only rational explanation. It also furnishes the only satisfactory explanation of the genesis of many of the so-called benign tumors. One great drawback to the acceptance of the embryonic theory has been the difficulty of scientific demonstration, both of the actual presence of the misplaced rudiments, and of the production of tumors by artificially establishing the conditions assumed as requisite. The possibility of the misplacement of embryonic cells seems, however, to have been demonstrated, and it is even known that such cells may retain their vitality through a considerable period of time. It has also been shown by competent observers that islands of cells (rudiments of tissues or of organs) may be found outside of their normal habitat in adult animals; *e. g.*, cartilage and bone in the tonsils, cartilage in the kidneys, epithelial structures in the uterine parenchyma, and the frequent presence of "rests" of such organs as the adrenals, thymus, and thyroid. With these facts in mind, it becomes quite reconcilable that the genesis of tumors tending to reproduce mature tissue-elements, and of those arising from rests of misplaced organs, should be explained by Cohnheim's theory. The great problem, however, that still remains, granting the possible existence of misplaced rudiments, is, What factor stimulates these aberrant cells or cell-colonies to produce a neoplasm? It is just here that speculation has been especially active. In this connection Ribbert's ingenious hypothesis may be mentioned. He holds that tumors arise both before and after birth from a partial or complete separation of cells or groups of cells from their organic continuity. Released from the influence of inclusion in the cell association these separated fragments (germs), if capable of increase, grow independently into tumors; provided, of course, they get into favorable surroundings and nutritive conditions. Depending upon the size and organization of the fragments the tumors may correspond in their main features with the parent organ, or they may differ from it in part or entirely. In the main, Ribbert attributes the genesis of tumors to mechanic isolation, the inherent properties of the isolated cells remaining unchanged during their proliferation. Here he is opposed by Hanseemann, who maintains that a change in the nature of the cell ("anaplasia") must precede its response to proliferative stimulus if it is to become a tumor and not merely take part in a simple hyperplasia.

But whatever may be said as to the bearings of the embryonic theory in relation to tumors in general, it certainly is apparent that even its warmest adherents do not urge it as fully explaining the origin of malignant neoplasms. The latter have so many distinctive characteristics, and their analogies with some of the growths arising from infection are so numerous, that a *parasitic theory* has been advanced for their explanation. The finding of micro-organisms, like bacteria, yeast, and possibly moulds, in these tumors naturally strengthened this hypothesis. So far as the bacteria are concerned, it may be said that they are at present no longer considered as the etiologic factors. Many forms of cell inclusions which were interpreted as developmental stages of lowly animal parasites (*Protozoa*, or more specifically representatives of the class *Sporozoa*) have been considered in the last ten years as causative agents. At present the general tendency is to renounce the sporozoan theory, and to lay the weight of responsibility upon *Blasto-*

mycetes, or yeast fungi. Pathologists of the Italian school are especially prominent as advocates of the blastomycetic theory.

So far as the sporozoan theory is concerned, it has met with two serious obstacles to its acceptance—viz., the recognition that many of the cell inclusions looked upon as parasites are degenerated red and white blood-cells, hyaline masses, vacuoles, outcast chromatin, engulfed cells, and various kinds of artefacts; and again by the absolute failure of all attempts to cultivate these so-called organisms outside of the tumor in which they were found, or to induce their multiplication in inoculated animals. In these respects the investigators working upon the blastomycetic hypothesis have been more fortunate, for they have not only successfully demonstrated the presence of yeast or budding fungi in microscopic sections of some tumors, but they have accomplished the cultivation of these fungi upon artificial media outside of the body. The vital link in the chain of etiologic evidence is still lacking in establishing the possible relationship of certain species of blastomycetes to tumor production; that is, the experimental reproductions of true tumors by the inoculation of pure cultures into animals. Several of these blastomycetic species have been shown to possess distinct pathogenic activities, producing in experimental animals nodules which macroscopically resemble true tumors; but on histologic examination these nodules prove to be mere granulation-tissue growths, such as are produced by inflammatory reactions to several kinds of infection. Up to the date of this writing, no satisfactory evidence has been adduced to show that anyone has successfully reproduced a tumor with all the morphologic features of spontaneous true tumors by inoculation with pure cultures of yeast organisms obtained from an original tumor. To say, however, that this demonstration is not to be finally accomplished would be unwise; and to assert positively that several of the varieties of tumors may not originate from infection with different species of parasitic micro-organisms is scarcely a justifiable attitude.

Another theory for the origin of tumors, of which only a hint is now heard, is what might be styled the *autotoxic hypothesis*, which assumes that the products of perverted metabolism in animal organs or tissues produce morbid effects in the individual's own body. This theory has been accepted as accounting for several obscure morbid processes, and it will not be surprising to find it prominently espoused in connection with the etiology of tumors; nor is it beyond the bounds of probability, from what we already know of the effects of certain substances originating in the animal economy, that in one or more varieties of tumor they may play an important part. As suggestive analogies, we have but to recall the often localized myxedematous deposits in hypothyroidism, the localized increase of elastic tissue in scleroderma, and the irregular overgrowth of bone in acromegaly.

THE SPECIAL VARIETIES OF TUMORS.

THE SO-CALLED BENIGN TUMORS.

Fibroma.—Both in their gross and microscopic appearance the neoplasms classed as fibromas have a close resemblance to connective tissue. They form more or less circumscribed masses, usually readily demarcated from the surrounding structures. While generally roughly spheric in shape, particularly when found in the substance of a soft organ, they may assume various forms. Growing from free surfaces, they tend to take a nodular shape, producing some of the so-called papillomatous growths; these papillomatous fibromas of the mucous surfaces are represented by certain polypi, seen in the nose, for instance; and on the cutaneous surface they produce warty growths. The diffuse thickening of the subepidermal connective tissue characterizing elephantiasis is regarded as a fibromatous metamorphosis; so also is the increase of connective tissue about the peripheral nerves producing the growths known as neurofibromas, which take various shapes, like the round or knob-like amputation-neuroma upon the ends of severed peripheral nerves, or the net-like series of nodular tendrils seen in the *cirroid* or plexiform neuroma (Rankenneurom).

As a rule, the fibromatous tumors are of exceedingly firm consistency, giving at once the impression of their fibrous character. But some of the neoplasms classed with the fibromas are very soft, as the *molluscum fibrosum*, or very friable, as the mucous polypi.

On macroscopic sections the firmer tumors present a white, glistening surface, in which the coarse fibrous bands can often be traced; in the softer kinds the section is more homogeneous, and fails to show the fibrous bands. Even in a single tumor the section may not always be uniform, since harder and softer areas, and cavities filled with gelatinous or fluid contents, sometimes are found.

As its habitat a fibroma may select any region of the body in which connective tissue abounds, although a predilection is shown for such localities as the skin, periosteum, fascia, uterus, and mammary gland.

The tumors of this variety are generally encountered singly; but they may be multiple. Among the subvarieties, like neurofibroma and *molluscum fibrosum*, a tendency to multiplicity is the rule, and hundreds of nodules may be scattered over the body, usually in the subcutaneous tissue.

In its minute anatomy a fibroma exhibits the structure of connective tissue, and, like the normal tissue, varies chiefly in accordance with its richness in cellular elements. In the denser tumors the cells are relatively few, and their nuclei are compressed laterally, making long, narrow bands with compact chromatin, which lie in the midst of well-developed fibers, appearing like those of mature normal fibrous tissue. The blood-vessels are relatively few, and the lymph-spaces narrow, explaining the white, dense, and dry appearance of these masses on section. Subvarieties with greater richness in cells, in blood-vessels and lymphatics are met; in the softer kinds, an appearance much like embryonic or newly forming connective tissue is at times produced. Here the nuclei are quite large, round, or oval; and the chromatin is present as a well-marked reticulum, in which one or more nucleoli appear. A distinct cellular protoplasm is to be defined in most fibromas; but in some of the harder kinds, especially those of keloid, in

which the structure resembles a coarse scar-tissue, the nuclei lie along the heavy fibrous bands making the bulk of the tumor-mass.

An important question relative to fibromas and other varieties of connective-tissue tumors is that concerning the development of elastic and collagenous substances in the groundwork. While some work has been done in this direction, particularly by Unna and his followers, the details as to the source of these tissue-components, their significance and fate, have not been accurately determined. According to Melnikow-Raswedenkow, tumors contain very little elastic tissue; no new formation of such tissue takes place in the substance of the tumor. But this view is not sustained, especially by recent studies of the American investigators—Alice Hamilton, Williams, and White—who find elastic fibers frequently present in tumors, either in the stroma, among the cells, around the blood-vessels, or around

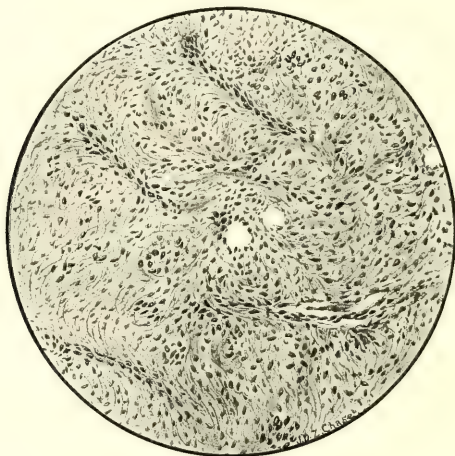


FIG. 53.—Soft fibroma. $\times 135$.

the milk-ducts in mammary neoplasms. This elastic tissue is usually in connection with the pre-existing elastic-tissue elements of the matrix, although new formation also probably occurs.

A richness in cells is not the only factor productive of soft fibromas; thus, in the mucous polypi the scanty cells with the delicate fibrils are widely separated by a deposit of mucin-containing material; and in other tumors serous fluid may accumulate in the substance, producing a softened, edematous condition.

The blood-vessels in fibromas, as a rule, show the ordinary histologic structure, but they may present distinct alterations, especially a thickening of the middle and external tunics, resulting in a narrowing of the lumen. Polymorphonuclear leukocytes and lymphoid cells are not numerous in fibromas unless inflammatory or degenerative changes are in progress, but mast-cells are often found in large numbers, particularly at the growing

borders of the tumor, and in those undergoing mucinous alterations. However, from the fact that these latter elements are found in several varieties of tumors, both benign and malignant, as well as in other pathologic tissues, it is hard to determine their significance unless, indeed, they be the forerunners of mucoid metamorphosis, as Harris has recently suggested on the ground of some very suggestive similarities in staining-reactions.

With the exception of the neurofibromas, nerves have not been demonstrated in this variety of neoplasm. In the case of the neurofibromas which may form in the cerebral, spinal, or sympathetic nerves or their ganglia, it is generally held that no new formation of nerve-fibers occurs. The tumor takes its origin either from the endoneurium of a peripheral nerve, pushing aside the nerve-fibers until they become widely separated, and even perish from pressure and disappear, or from the perineurium or epineurium, growing laterally from the original nerve-trunk, sometimes surrounding it without disrupting the natural arrangement of the nerve-fibers. It is therefore clear why a histologic study of the neurofibromas, as found in the skin and along the course of peripheral nerves, should show gradations relative to the nerve-fibers, which sometimes are abundant, again isolated or even absent, and why these fibers vary from apparently normal medullated fibers to naked axis-cylinders, or axis-cylinders variously deformed.

The rate of growth of fibromas is usually slow, although not invariably so. Those richest in cells with well-developed cytoplasm and nuclei grow most rapidly. It is rare to find nuclei in any of the stages of mitosis; and it is quite probable that even in the more rapidly growing forms the type of nuclear division is a direct segmentation or amitosis.

The pure fibromas have no capability of reproducing true metastatic growths, and in most instances a recurrence after thorough removal by operative measures is impossible. An exception to this rule is found in keloid, especially in the spontaneous variety, in which the tumor recurs after thorough and repeated attempts at removal.

Inflammatory reaction, although rare in fibromas, may follow infection with pyogenic bacteria. Various metamorphoses or degenerations to which connective tissue in general is predisposed, such as mucoid or myxomatous, fatty, and edematous, may take place in these tumors. In fibromas of uterine origin cysts are sometimes found, and a cystic condition is not uncommon in the tumors originating in the mammary gland.

That some fibromas owe their origin to traumatism as one, at least, of the inciting factors seems definitely established, and is exemplified by the fibromatous keloid which develops in scar-tissue after injury or operation. A predisposition of the skin to fibromatous overgrowth, especially in the form known as spontaneous keloid, seems especially pronounced in the victims of a syphilitic or leprous taint, and in the colored race. Fibromas are also encountered as congenital growths, and in some cases an hereditary predisposition seems to exist, particularly with reference to keloids and neurofibromas.

Lipoma.—There is no special difference in the structural characteristics of lipomas and ordinary adipose tissue. In gross appearance these tumors simply present the characters of a localized mass of fat, in no way different from the normal subcutaneous fat. The microscope reveals the same resemblance, and the fat contained in these neoplasms responds to the usual chemical reactions of this substance. It was these points of similarity

which led to the assumption that lipomas took their origin in pre-existing adipose tissue.

The size of lipomas is subject to variation, certain of the neoplasms, especially those in the kidney and liver, being barely recognizable without microscopic aid; while others, especially the pendulous tumors seen about the neck and shoulders, may become massive. They are generally rather soft and yielding. In most cases the contour is regular, the formation of accessory nodules not being so common as in other new growths. A rigid respect for surrounding structures is ordinarily shown, and usually a fibrous capsule sharply isolates the fatty tumor from the structure in which it grows.

The subcutaneous tissue, especially about the back, shoulders, axillæ, and groin, is the favorite seat of fatty tumors. The viscera—in particular the kidneys, rarely the brain—may be affected. The tumors appear both in fat and lean individuals, generally in adult life; although they are to be found in children, and even appear as congenital growths.

The majority are solitary. However, multiple lipomas reaching considerable numbers have been described. Another curious variation in the appearance of fatty tumors is a symmetric disposition of two or more masses in the body, as, for example, in both groins and both axillæ.

Lipomas grow slowly and produce no disturbance, except by pressure or by mechanic interference.

Inflammation following infection, even leading to abscess, is a possible, though not a common, occurrence in fatty tumors. The fat in certain portions may soften, and by liquefaction an oil-cyst may be produced. An overgrowth of fibrous tissue makes a firmer tumor, usually designated a fibrolipoma, and a mucoid metamorphosis may occur in portions of a fatty tumor, making a myxolipoma.

A peculiar form of fatty tumor, the nature of which is not well determined, is the *xanthoma*. The xanthomas are usually small yellowish tumors with fat-containing cells, and are either located in the eyelid, or as multiple disseminated growths beneath the skin, or even in the internal organs, as the trachea, pericardium, splenic capsule, or the liver. Whether they originate from pre-existing fat-cells, or from a transformation of endothelial cells of the lymph- or blood-channels, is not determined; some believe that they may arise from a local bacterial infection. One peculiar feature of the xanthomas is the presence of multinuclear giant cells. They are sometimes met with in diabetic persons, having apparently some relation to the disease, "*xanthoma diabeticorum*."

There is no doubt that some lipomas originate as the result of injury. This is seen in the tumors appearing on the hands of working-people, in the portions most exposed to traumatism. These tumors have also been found springing from scar-tissue. In the case of the symmetric lipomas particularly, a nervous (trophic) influence is supposed to play a part. The embryonic origin of this class of tumors seems clear in the case of their appearance in infants and young children; fatty or lipomatous tissue, moreover, makes a large bulk of many teratomas.

Chondroma.—Tumors having a macroscopic and microscopic resemblance to cartilage are designated as chondromas or enchondromas. These growths vary in size, the smaller masses being nearly spheric, while the larger are irregular, nodular, or lobulated. A capsule of fibrous tissue generally serves to bound the chondromas. The tumor presents a homogeneous,

cartilaginous aspect on section ; the larger masses may contain softened foci, and even cystic cavities filled with gelatinous material.

In minute structure an appearance more or less resembling normal cartilage is presented. The cells may be encapsulated or free, and are spheric in shape in most cases, sometimes large and again small. Oval, spindle-shaped, and branching cells appear in some specimens. The cellular elements may be closely and evenly set, widely separated, or aggregated in groups of varying size. The ground-substance may be hyaline, like hyaline cartilage, or more or less reticulated, like fibrocartilage. Foci of beginning ossification or of mucoid or fatty metamorphosis are quite common. Even in the hyaline variety the cartilage is isolated into islands, surrounded by fibrous tissue, which carries the nutrient vessels.

Chondromas may appear in situations in which cartilage exists normally, as about the articulations and in the trachea ; on the other hand, they not

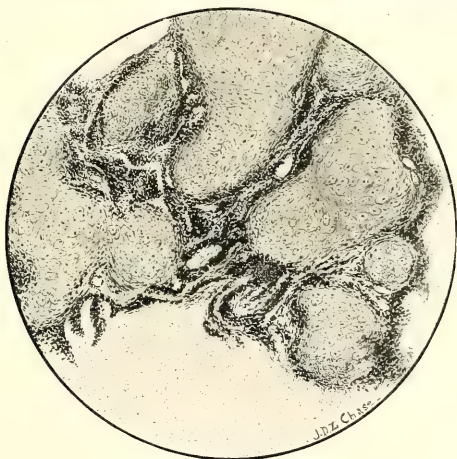


FIG. 54.—Chondroma of the lung. $\times 35$.

uncommonly arise in localities in which cartilage naturally is absent, as in the substance of well-developed bones, in the parotid gland, the testicles, the mammae, and even, in rare instances, in the skin. Multiple chondromas occur especially on the hands.

The pure chondroma is a tumor of slow growth. Its influence upon surrounding structures is mainly a mechanic one. This rule is not without exception, for certain varieties, instead of growing symmetrically and ignoring the surrounding tissues, send islets of tumor-cells into the tissue-spaces, especially in connective tissue and muscle, even for some distance beyond the principal tumor-mass. Finally, in rare cases, tumor-elements may be transported by the vascular channels, probably through invasion of the vessel-walls, secondary growth or metastasis being set up in distant parts of the body. Even in chondromas the morphology of which seems identical with the ordinary benign forms this may happen. These malignant

cartilaginous tumors are not to be confused with the mixed forms, in which sarcomatous elements predominate (*chondrosarcoma*).

In the development of cartilaginous tumors in regions which normally contain cartilage, it is only necessary to conceive of their origin from the cells previously existing, though little is known of the forces by which the proliferation of such cells is brought about. In the case of tumors which appear in fully developed bone, Virchow's theory is generally adopted. He holds that in these cases islets of cartilage were misplaced in the post-embryonic development of the growing bone, generally through rachitic changes, and that from these islets cartilaginous tumors later arise. The foci situated in the spongy portion of the bones form true chondromas, those in the more compact portions cartilaginous-osseous tumors or chondro-osteomas, while in the dense bony tissue pure osseous tumors develop. To account for the appearance of chondromas in tissue which never contains cartilage normally, the theory of misplacement of embryonic rudiments offers the only acceptable explanation.

Aside from the mixed forms of cartilaginous tumors (osteochondroma, myxochondroma, lipochondroma) brought about by the metamorphosis of portions of the tumor itself, a very interesting neoplasm related to the true chondroma, at least so far as genesis is concerned, should be here noticed. This tumor, described by Virchow as *echondrosis physalifera*, or better designated as *chordoma*, apparently has its origin in abnormally persistent remnants of the embryonic notochord, or *chorda dorsalis*. The most common situation is beneath the dura of the clivus (*clivus Blumenbachii*) of the body of the sphenoid bone, or about the junction of the body of the sphenoid bone with the occipital. This region represents the anterior extremity of the notochord. These tumors may also appear in the bodies of the vertebra. They are generally small (cherry size), and show on microscopic examination a series of large vacuolated cells with poorly defined boundaries, sometimes closely packed, and again separated by a homogeneous, structureless substance. The histology of these tumors closely resembles that of the remains of the chorda found by an examination of the region of the clivus under normal conditions.

The chondromas of the testicle and of the parotid gland are nearly always associated with other forms of tumor-tissue; hence they are called mixed tumors. Reference will be made to them later.

Osteoma.—Osteomas are tumors composed of osseous or bony tissue, either hard and compact or soft and spongy. They are situated in various parts of the body, either in connection with pre-existing bone or independently of it. They vary in size, the harder variety, which is usually multiple, being small, while the spongy bony tumor often reaches a large size. The microscopic anatomy of these tumors is essentially identical with that of various normal types of bone. It is often difficult to draw a sharp line between the chondromas and tumors containing osseous tissue, since they often merge into each other.

The process of ossification in bony tumors proceeds in the same way as in developing bone. Many of the smaller tumors of ivory-like hardness remain stationary after attaining a certain size. Ossification proceeds as a metaplasia, as seen in the transformation of cartilage and cartilaginous tumors into osteomas; as a reversion to former functional activity, seen in the dura of the cranium and of the spinal canal, which resumes its periosteal

or bone-forming function; or finally these tumors may arise by proliferation of elements the origin of which is unknown.

Bony tumors occur in connection with the skeletal system in any part of the body, as subperiosteal growths in connection with the bone, making surface protuberances, or in the bone-substance proper, or within the bone-cavity. Bony tumors growing upon the surface of bones are designated as *exostoses*, and are ivory-like in density or softer and more spongy, or even partly cartilaginous in some cases. Many bony new formations are, strictly speaking, not true tumors, inasmuch as they are the direct result of irritation and inflammatory action. It is, however, difficult to draw the line between osteomas and such bony growths, which are often designated as *hyperostoses*. True bony tumors not rarely occur symmetrically.

Osseous tumors arise in connection with the teeth, either from the enamel, the dentine, the cement, the tooth-follicle, the fibrous tissue about the teeth, or from the tooth-structure as a whole. To these tumors the general term *odontoma* has been applied.

Pre-existing cartilage may furnish the nidus for the development of bony tumors. Osteomas also appear in various soft parts, like the tendons, fasciæ, muscles, and very rarely in the skin and the viscera.

The multiple osteomas of bones are related to multiple enchondromas, and it is possible that, like the latter, they originate from misplaced foci due to errors in the normal process of bone-formation, as seen in rickets. A strange occurrence is the production of metastatic bone-tumors from original non-osseous neoplasms of the adrenals, mammary gland, thyroid, and prostate.

Myxoma.—A variety of connective-tissue tumor closely related to the preceding forms, and scarcely worthy of a special classification, is the so-called myxoma, or mucoid tumor. A myxoma in the sense of a tumor composed purely of myxomatous or mucoid tissue is really not known, since all tumors of this class shade more or less into other forms of connective-tissue neoplasms, particularly into the fibromas.

The myxomas are soft, gelatinous, spheric or lobulated tumors, varying in size in different situations. They are generally sharply defined from the surrounding tissues, and when growing from free cutaneous or mucous surfaces are often pedunculated, forming one variety of the so-called polypi. On section a moist, shining surface is presented. Their consistency is not uniform, especially in the larger growths, since denser bands or isolated areas are present in the midst of the soft, jelly-like mass.

Microscopically the tumors are composed of spindle-shaped or star-shaped connective-tissue cells, separated by clear spaces which with ordinary reagents do not stain, but by treatment with special staining reagents having an affinity for mucin (*e. g.*, thionin) show more or less of this substance. The amount of this intercellular material varies, not only in different tumors, but also in different portions of the same tumor.

The softer polypi found in the nose and ear are myxomas. Tumors of this class are also found in the skin, bone-marrow, mammæ, peripheral nerves, the brain and spinal cord, and occasionally in other viscera (the heart and kidneys). The *hydatidiform mole* is regarded as a myxoma of the chorionic villi.

A myxoma grows with moderate rapidity. It possesses no power of metastasis.

Except in the congenital type of these tumors, the structure of which is

quite similar to the gelatinous substance of the jelly of Wharton in the umbilical cord, the myxomas apparently owe their origin to an edematous metamorphosis of a connective-tissue tumor. From some circulatory disturbance, or in some cases from an abnormal thinness of the blood-vessels, a serous fluid transudes into the meshes of the tumor, pushing apart the cells. This fluid is very similar to that found in ordinary edema of subcutaneous tissues, and the microscopic appearance of a myxoma is much the same as that of edematous connective tissue. The presence of mucin in this serous transudate is a matter of dispute, certain observers holding that true mucin is absent both in ordinary edematous tissue and in the myxomas.

Taking the view that an edema underlies the development of myxoma, it is easy to reconcile the various mixed types of tumors in which myxomatous tissue is present. The softer forms of fibroma are on the border-line with a moderate edema, while a localized edema, more or less rich in mucin, gives

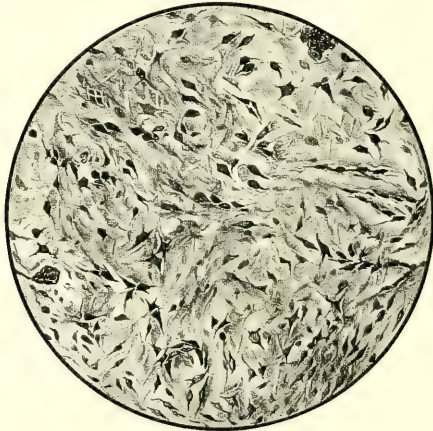


FIG. 55.—Myxoma. $\times 160$.

in lipoma, chondroma, osteoma, and occasionally in sarcoma, the mixed tumor-forms designated as myxolipoma, myxochondroma, myxo-osteoma, myxosarcoma.

Myoma.—Muscles, both of the striated and the unstriated variety, may constitute the principal component tissue in a class of tumors described as myoma. Those comparatively rare myomas composed of elements resembling striated muscle are called rhabdomyomas, to distinguish them from the more common variety with unstriated muscle-fibers, the leiomyomas.

Rhabdomyoma.—In gross morphology there is nothing strikingly characteristic about the striped-muscle tumors, which vary considerably in size and shape, even forming polypoid masses when situated on free surfaces. While occurring in those localities in which striated muscle is normally present, the rhabdomyoma more often selects organs naturally devoid of striated muscle. The genito-urinary tract is a favorite seat for these striped-

muscle tumors (the kidneys in particular), more than half the recorded cases being confined to this system. Less frequently the cervical and orbital regions are involved, while the skeletal muscles, connective tissue, mediastinum, heart, and esophagus are still more rarely chosen. It is important to note that rhabdomyomas appear most commonly in early childhood, and that they have even been found in the newborn.

Two principal kinds of mesodermic tissue make the histologic basis of these morbid growths, a vascular connective-tissue framework, and an imperfectly developed striated muscle. The framework varies in amount in different tumors and in different portions of the same tumor, and it further varies in the richness of its cells and fibers, often complicating the structure of the tumor by its irregular behavior. A noteworthy point concerning the morphology of the myomatous tissue is that it *never attains the full development of mature striated muscle*, always stopping short of the production of perfect fibers with regularly disposed sarcous segments. Indeed, the distinguishing histologic feature about these tumors is the immaturity of the component fibers, which strongly recall the various stages of developing or regenerating striated muscle-fiber never reaching completion. The fibers may attain considerable length and show quite regular and prominent transverse striae, or there may be both transverse and longitudinal markings. The nuclei may be flattened and disposed alongside the fiber in a manner somewhat recalling that seen in well-developed voluntary muscle. Other fibers are shorter, irregular in contour, often spindle-shaped, and show uneven transverse markings or none at all, while longitudinal lines may or may not traverse them. In these fibers the nuclei are often abundant, and sometimes large and vesicular, rich in chromatic substance, and disposed along the middle of the fibers. Finally, masses of sarcoplasm with chromatin-rich nuclei, entirely undifferentiated, are encountered. Probably the excess of these spindle, oval, and round cells in certain tumors led several observers into the error of considering them to be connective tissue or sarcomatous elements, resulting in the designation of these tumors as rhabdomyosarcoma. It is distinctly more appropriate to regard these cells as undifferentiated or embryonic muscle, since they correspond so perfectly to such cells seen under normal conditions of development or repair, although the occurrence of rhabdomyoma and sarcoma in combination is not to be denied. A further argument for the embryonal nature of these elements seems to be afforded by the frequent presence of glycogen droplets, both in the muscle-cells and the connective tissue. Islets of cartilage, of bone, of adipose tissue, and even of epithelial gland-like structures have been discovered in rhabdomyoma; and myomatous tissue such as has just been described is a not uncommon constituent of certain complex teratomas, especially those of the kidney and testicle.

As to the origin of the rhabdomyoma, it is now generally conceded that it is a neoplasm of embryonic aberration. Both the frequency of these tumors as congenital or infantile formations, their site in regions particularly involved in complicated embryonic foldings and shiftings, and the embryonal nature of their essential cells make this view a reasonable one. Recalling the part taken by the various rudiments in the formation of the kidney, it is not difficult to comprehend how a misplaced myotome or portion of a myotome could furnish the matrix from which a rhabdomyoma later developed; and with a participation of the sclerotome and nephrotome those more complex tumors with striated muscle, cartilage, and epithelial structures could

be explained. In the case of a rhabdomyoma of the myocardium, it has been shown that the tumor-elements reproduce, in their form and arrangement, the histologic picture of the heart-muscle of a four weeks' human embryo.

Liomyoma.—The type of this neoplasm is the familiar growth commonly and erroneously called "uterine fibroid." Some of these tumors are of enormous size, while others are minute. Both single and multiple liomyomas are found. The large uterine tumors are not infrequently nodular, while those found in the intestine may have a polypoid shape. The tumors are generally firm, white or pinkish in color, and glistening on section, in which close inspection will reveal the component fibrous strands travelling in different directions. It may show a cystic metamorphosis (*cystomyoma*), or the fibrous connective tissue may predominate, producing a hard tumor called a fibromyoma. By far the greater number of tumors of this class are found in the uterine musculature, especially after the onset of puberty. It is very rare to find them in the uterus of children, and they seem to be unknown as congenital formations. The alimentary tract is also a favorable location; occasionally they are found in the urinary bladder, urethra, and the larynx. In the skin, where they are at times met with, their origin seems to have been traced to the erector muscles of the hair-bulbs.

Smooth, spindle-shaped, nucleated muscle-fibers aggregated into narrow bundles and running in various directions in a more or less abundant connective-tissue stroma make up the essential histologic structure of these tumors. Maceration in 20 per cent. nitric-acid solution produces dissociation of the myomatous elements and permits their study as individual cells or cell-groups; but for tracing the muscular strands and for finer study, thin, well-stained sections are requisite. A point worthy of attention relates to the presence of blood-vessels in the center of these muscular bundles, especially to be seen in the smaller uterine nodules, and the interweaving muscular strands frequently pursue the same tortuous course as the vessels. This discovery has led to the conclusion that many of the liomyomas have their primary origin in the proliferation of the unstriped cells of the arterial muscularis; and certainly this view seems to fit most uterine myomas, and seems also applicable to those of the gastro-intestinal canal and to those dermal myomas which cannot be traced to the erector muscles.

The simple histologic structure of the muscle-fibers and connective tissue is sometimes complicated, especially in the tumors originating in the uterus, by epithelial cells in groups, in imperfect tubules, or lining cystic cavities. Their histogenesis is not fully determined, and they have in turn been ascribed to aberrant remnants of Gärtner's duct, Müller's duct, and of the Wolffian bodies. It is more likely, however, that the epithelial elements are derived from severed portions of the uterine mucous glands, which sometimes penetrate beyond the normal confines. In one case of myoma of the stomach, remnants of misplaced pancreatic tissue were recognized.

Many of these new growths contain mastzellen in abundance, sometimes in the proper muscular tissue and again in the tissues bordering the tumor. The significance of these peculiar granular cells in connection with liomyoma is entirely a matter of conjecture.

Obscurity surrounds the question of *etiology*. Transposition of embryonic rudiments may account for certain of the liomyomas, but not for all. In one case it was thought a diabetic dyscrasia provoked the appearance of

multiple dermal myomas; and the possibility of syphilitic influence has also been suggested.

Lymphoma.—The lymphadenoid tissue of the human body reacts to a variety of physiologic and pathologic impressions resulting in a proliferation of lymphoid cells which remain localized in the gland in focal accumulations, producing lymphadenoid hyperplasia and hypertrophy, gain access to the circulation, appearing in the blood as a lymphoid leukocytosis, or produce both lymphatic enlargements and lymphocytosis. Of the morbid influences leading to regional or general lymphadenoid overgrowth (with or without lymphocytosis) a number may be cited, as, for example, various acute and chronic infections, and the hematic dyscrasias designated leukemia and pseudoleukemia. In some of the latter class of cases lymphatic tumors, or lymphomas, may be produced, sometimes localized, again general. Enormous single lymphomatous tumors may appear, like those seen in the mediastinum, accompanied by multiple enlarged lymph-glands and the overgrowth of lymphoid cells in viscera like the kidneys. Such occurrences are often called “malignant” lymphoma, or lymphosarcoma, and the clinical and anatomic picture is enough like that exhibited by other malignant tumors to justify the appellation. However, these neoplasms are regarded as in some way induced by a perversion of the blood-forming organs, probably incited by an infectious or a toxic agency, and are therefore to be excluded from tumors proper. A clear distinction between the various pathologic conditions of the lymphatic system comprehended under the terms lymphoma, malignant lymphoma, leukemic lymphoma, aleukemic lymphoma, and lymphosarcoma cannot now be drawn.

Whether there is such a thing as a true lymphoma, a growth originating from and composed of the proper lymphoid cells, and imperfectly reproducing lymphatic structure independent of a localized or general infection, or of a disease of the hematopoietic system, is very doubtful. Such a tumor is described by some authors, but without sufficiently sharp distinctions. In other cases, especially with the solitary benign lymphomas which show enlarged lymph-nodes, the possibility of an infectious origin has not been ruled out. But it may here be appropriate to remark that we cannot be too critical regarding this type of neoplasm, for if we are to eliminate those tumors in which an infectious cause is suspected, and retain as true tumors only those in which an embryonic or non-infectious postnatal causal influence can be proved, then lymphoma, as just described, will appear in a goodly company.

Angioma.—Tumors composed of vascular elements in preponderance are designated as angiomas, and those of blood-vascular origin are usually separated as hemangiomas from those of lymph-vascular origin, which are called lymphangiomas.

Hemangioma.—Several varieties of blood-vascular new growths are encountered, and in some of them it is not clear whether the tumor really results from a new formation of blood-vessels or from a dilatation or hypertrophy of blood-vessels originally present. The diffuse reddish or purplish and slightly raised tumors often present as birthmarks and characterized as *nevi* or *telangiectasia*, belong to the doubtful formations, as they have in some instances been shown to be due to locally dilated capillaries. Another variety of these tumors is composed of communicating spaces filled with blood and bounded by partitions of purely connective-tissue origin; these

are the *cavernous angiomas*. But besides these doubtful forms, hemangioma occurs as a true tumor composed in bulk of newly formed blood-vessels, and these vessels may originate from the arterial, venous, or capillary system. One form of arterial angioma, from the thickened and tortuous development of its vessels, is known as a *cirroid aneurysm* or *plexiform angioma*.

Hemangiomas appear as diffuse (often widespread) growths, or in circumscribed nodules, either beneath the surface or projecting from it. On account of the contained blood they usually can be readily recognized by their red color, and in the tumors projecting from a free surface, *e. g.*, the scalp, a tendency to free hemorrhage after even slight traumatism is characteristic. A distinct pulsatile expansion is sometimes noted, particularly in the nodular forms.

The microscopic anatomy of the hemangiomas varies according to the

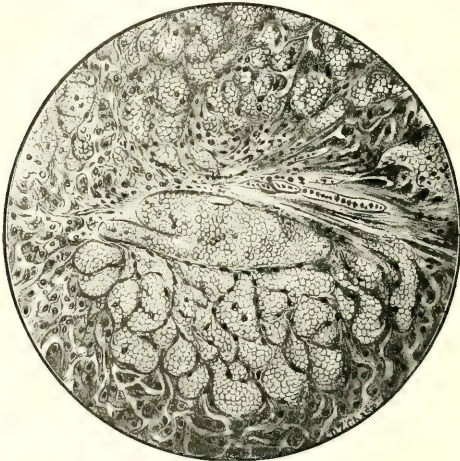


FIG. 56.—Cavernous angioma of the liver. $\times 135$.

nature of the new growth. In the tumors with venous or arterial vessels their structure is quite similar to those vessels found normally in the body. In the nevi the vascular channels have somewhat the structure of capillaries, with a thickening of the walls and dilatation of the vessels. Groups of these vessels, surrounded by connective-tissue septa, are found beneath the skin, covered superficially by intact epidermis, and appearing in situations normally occupied by fat lobules. Here and there, in the midst of the group of vessels, hair-follicles, sweat- and sebaceous glands can be seen. The vessels composing these groups have endothelial walls, usually several cells deep, and surrounded by a poorly defined basement-membrane. That active proliferation is going on in some, at least, of this variety of angioma is evident from the presence of karyokinetic figures in the cells of the vessel-wall.

The *nodular angiomas*, usually projecting above the skin, show a very irregular development of blood-vessels. Sometimes they appear as capillaries with greatly thickened walls, with little intervening tissue; again the walls are thin and composed of little more than a single layer of endothelial cells. Finally, the vessels may be considerably dilated (often irregularly), and partake of the nature of poorly formed venous channels.

In the *cavernous angiomas* the masses of blood, varying greatly in size, appear in spaces bounded by thin walls which exhibit the structure of connective tissue and are lined with endothelial cells. The peculiarity of the vascular structure seen in the walls of these cavities has led Ziegler to regard these formations as separated from true tumors. In a multiple cavernous angioma of the liver he was able to trace the original tumor to the dilatation of a single capillary, and to consider the resulting growths as due to a cavernous metamorphosis of the liver-lobules. Besides the blood-elements in normal proportions, an excess of leukocytes can be found in some of the cavernoma, and a deposition of fibrin-threads and the formation of thrombi may be encountered. Either from their escape into surrounding tissues (hemorrhage) or from stagnation in the angiomatous spaces, the blood-cells may perish and remain as foreign bodies, calling into play the process of phagocytosis in their removal. Leukocytes and the offspring of the fixed tissue-cells appear in and about the angioma, loaded with blood-corpuscles in various stages of disintegration or with hematogenous pigment. Occasionally these scavenger cells become so numerous as to give the tissue an aspect suspicious of a sarcomatous or melanosarcomatous growth, seriously complicating the histologic picture. It is almost superfluous to add that a similar phenomenon is seen in other varieties of tumors in the event of hemorrhage or death of red blood-cells.

The diffuse angiomas, or teleangiectases, are usually found in the skin, especially of the head and neck, and for the most part are congenital in origin or appear shortly after birth. Some of these formations occur at points at which clefts unite during fetal life, and they are therefore designated fissural angiomas. Diffuse hemangiomas are occasionally met in the muscles, the breast, and the viscera. The skin is also the seat of the majority of the nodular angiomas, and a tendency to multiplicity is by no means uncommon. A particular kind of multiple nodular hemangioma of the skin is found in old people—the so-called senile angioma. Cavernous angioma may also appear in the skin; but it is more often located in the viscera, especially the liver. Both the nodular and the cavernous hemangiomas have been found in various organs of the body, including the central nervous system, and even in the bones.

As to the etiologic factors concerned in the formation of these tumors, we must admit that developmental or embryonic influences play a prominent part in many of the diffuse congenital neoplasms of childhood. Traumatism is also an important agent in favoring the development of certain hemangiomas, and such factors as variation in the blood-pressure and the velocity of the blood-flow and obstructive agencies must, as Thoma has pointed out, take a prominent part. The cavernous angiomas of the liver are usually well circumscribed by a fibrous capsule; this, among other features, has led Ribbert to look upon them as due to the development of preformed congenital structures.

Lymphangioma.—As is the case with the blood-vascular tumors, so the lymphangiomas are doubtless of two kinds—viz., true tumors in which new growth of lymph-vessels takes place, and tumors arising from dilatation of pre-existing lymph-channels or from their hypertrophy; and, like the hemangiomas, we find subvarieties of the lymph-vascular neoplasms depending upon morphologic peculiarities. Thus there is a diffuse new formation of lymph-vessels, or a widespread dilatation of pre-existing vessels producing a *lymphatic teleangiectasis*, and another form with irregular spaces, making a *cavernous lymphangioma*. In still another form distinct cysts are present—*cystic lymphangioma*; and sometimes these cysts contain chyle—*chylangioma*.

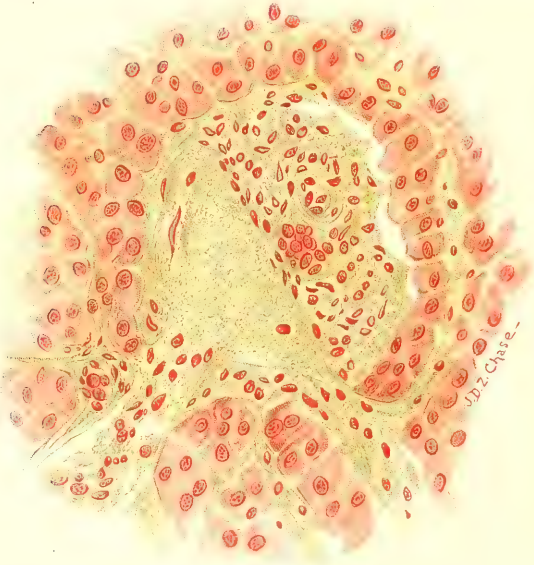


FIG. 57.—Lymphangioma of the liver. $\times 500$.

A diffuse lymphangiomatosis, when present in the tongue, is technically styled macroglossia, in the lip macrocheilia, beneath the skin of the neck hygroma; and in the skin this formation is known as a lymphatic nevus. Sometimes the cutaneous lymphatic nevi are pigmented. A local dilatation or hyperplasia of lymph-vessels more or less diffuse is the essential pathologic condition in certain well-known pigmented birth-marks; and to the same category freckles and certain cutaneous warts belong.

Both the diffuse and circumscribed lymphangiomas may attain considerable size, and in the cystic and cavernous varieties the tumors are often multiple. The contents of the tumor may be clear lymph; or this fluid may be

cloudy, and contain lymph-corpuses, or even blood-elements. Sometimes the fluid is partially or completely coagulated or solidified.

Histologically these tumors are characterized by their resemblance to lymph-vessels or lymph-spaces found in healthy tissue. A series of communicating clefts or spaces abound, which are lined with endothelium and surrounded by a more or less perfect framework of connective tissue, which is usually well supplied with cells. Scattered through the connective tissue islands of small round cells (lymphocytes) often abound.

The favorite seat of this variety of neoplasm is in the skin or subcutaneous tissue. They are more rarely found in connection with the digestive tract, and very rarely in the peritoneum and viscera.

Many of the lymphangiomas are congenital in their origin, as seen in

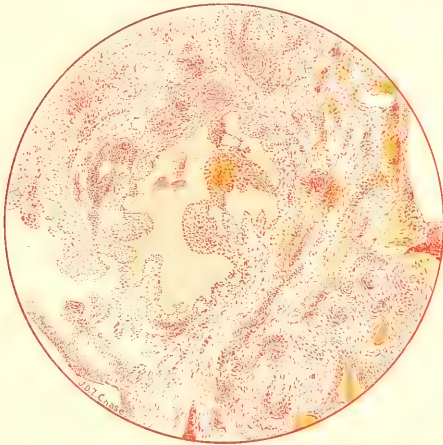


FIG. 58.—Lymphangioma of the skin. $\times 35$.

macroglossia and in pigmented moles or birthmarks; and this observation also holds true for the cystic and cavernous varieties. It would also seem that developmental errors are responsible for the origin of these formations. The tumors of this class may also appear any time after birth, some instances of their development in old age having been noted. As has been remarked, some of these formations must be regarded as diffuse or localized dilatations of pre-existing lymph-channels, and here the important factors must be the obstruction or stagnation of the normal lymph-circulation. Thus the chylangiomas probably are cysts originating in some interference with the normal output of Lieberkühn's glands in the small intestine (Lubarsch). However, there can be no doubt that in many of the lymphangiomas, both in the congenital and acquired forms, an actual new formation of lymph-channels takes place, though by what agency we cannot say.

In both the pure hemangiomas and the lymphangiomas the growth is benign; but since these tumors are largely composed of newly formed endo-

thelial elements, they are brought into proximity with a variety of sarcoma (endothelioma) which is of a destructive nature; and the gradation from a simple blood-vascular or lymph-vascular neoplasm to one or another of the forms of endothelioma is sometimes encountered, and is difficult to recognize histologically.

The Fibro-epithelial Tumors.—This is a class of tumors with two chief varieties and numerous subvarieties, about which considerable confusion still exists, especially when the attempt is made to classify them according to some rigid system. They are tumors in which connective tissue as well as epithelial elements are found side by side, both tissue-elements taking part in the new growth. Sometimes one and sometimes the other essential tissue type predominates. In those cases in which the connective tissue grows to predominate and the epithelium simply keeps pace to furnish the cover for the connective-tissue sprouts, it is evident that we are brought close on the border-line of such connective-tissue tumors as fibroma and myxoma, which grow from a mucous or cutaneous surface and obtain a covering of surface epithelium. Again, in those tumors in which the purely epithelial elements are largely in excess, the confines of certain kinds of malignant epithelial neoplasms (carcinomas) are reached. It should then be borne in mind that with the present class of tumors, as in many other varieties, absolutely specific differential characteristics cannot be set up. For this reason Ribbert's plan of describing under one common head the several varieties of this class of tumors has been adopted, since it does not commit itself to any particular scheme of classification.

The fibro-epithelial tumors, for convenience of description and for the purpose of utilizing the generally accepted terminology, may be divided into two principal varieties, based upon morphologic and histogenetic grounds. Those tumors in which *surface epithelium*, either cutaneous or mucous, participates, form one variety represented by the *papillomas*; while the neoplasms whose epithelium is derived from pre-existing glands or glandular remnants form the other main variety, the *adenomas*.

Papilloma.—For the most part the tumors belonging to this subdivision are, as the name indicates, "papillary" growths; that is, they tend to assume the form of a villous excrescence, projecting in the shape of a compound nodular mass above the surface from which they originate. In some of these tumors, especially those springing from the mucous surfaces, the growth is composed of a great number of delicate branching processes. The base of attachment of these masses is usually broad, though in some cases a very narrow pedicle serves to attach the tumor-mass to the surface from which it springs. Others of the papillomas are single protuberances, varying greatly in size. Again, there is a flat papilloma in which the tumor-mass is but little elevated above the surrounding surface.

Both hard and soft papillomas are found, those growing from cutaneous surfaces, like the common wart and the horny tumors, being generally more firm than those springing from mucous surfaces, although hard tumors are, for instance, found in the larynx.

As has been said, these tumors are usually situated on cutaneous and mucous surfaces, and are common in the skin at the orifices of the body, in the respiratory tract (especially the larynx and trachea), in the digestive tract, in the peritoneum, and in the genito-urinary tract. They are also found in the ducts of various glands. In the skin the ordinary examples

of the hard variety of tumors are the common wart, the dense cutaneous horns (*cornu cutaneum*), and the acuminate condylomas. Cauliflower-like growths seen in the urinary bladder and in the rectum are good examples of the soft papillomas; and the stomach and intestines are sometimes the seat of flat, papillomatous growths. Certain cysts, especially of the ovary, may become the seat of papillomatous growths in their interior.

The rate of growth in the harder tumors is generally slow, and they tend to remain at rest after attaining a certain size. Some of the soft, villous tumors grow rapidly, and become large enough to cause mechanic discomfort.

In structure these tumors consist of a vascular connective-tissue framework, upon which the epithelial elements are laid. The amount of this epithelial covering is subject to wide variation, and according to the locality from which the tumor springs we may find squamous or columnar epithelium covering the single or multiple connective-tissue sprouts. In the hard tumors of the skin the pavement epithelium is usually abundant, many-layered, and in various stages of horny transformation. In the soft, villous tumors the epithelial lining is thinner, sometimes being but a single layer of cells, and often these cells are but loosely attached to the supporting framework. This disproportionate relationship of the connective tissue and epithelium has given rise to the question whether the one or the other tissue forms the starting-point of the tumor.

That irritation, especially if long continued, is a potent factor in favoring the growth of certain of the papillomas is clearly proved. The condylomas or venereal warts appear especially about the penis, vulva, and vagina when these parts are the seat of an irritating venereal discharge or when some chronic inflammatory process is at work. It is highly probable that they owe their origin to some infectious agent, the nature of which is still obscure. Irritative factors can also be traced in some of the cutaneous warts and horns, and in certain cases a chronic inflammatory condition seems to underlie the development of papillomas in the larynx, the rectum, and the vagina. As congenital tumors the papillomas are rare; they have been found both in newborn and very young children, but an embryonic influence is hard to trace.

Adenoma.¹—In both macroscopic and microscopic morphology these tumors tend to reproduce the structure of glands or gland-like organs; that is to say, they are formations in which epithelium tends to arrange itself either in the form of tubules (*tubular adenoma*) or in acini (*acinous adenoma*), and in which the vascular connective tissue arranges itself to conform to the type of growth chosen by the epithelium.

Adenoma may grow in the substance of a glandular organ, and either take the type of the matrix or one foreign to it. It may also grow from free cutaneous or mucous surfaces. In the first instance it generally appears

¹ At first sight it seems easy to define as adenomas those tumors which tend to reproduce in their growth one or another of the types of glandular organs; but, as Lubarsch remarks, it is highly desirable, in accepting this definition, to be quite clear upon our definition of a "gland," and here an obstacle is encountered. Such secretory organs as the mammary, sweat-, and salivary glands, with the pancreas, liver, and glands of the digestive mucosa, are easily reconciled with our notions of what a gland really is; but in connection with the kidneys, adrenals, thyroid, hypophysis, the ovaries, testicles, and genital ducts, difficulties are met; in all these organs the characteristic elements may form tumors that are classed as adenomas. This shows how unsatisfactory the morphologic basis of definition and classification of tumors often proves.

as a more or less spheric mass, surrounded by a capsule. Upon free surfaces it tends to become compound, warty, or villous, resembling a papilloma, and usually styled papillomatous adenoma.

Depending upon the abundance and characteristics of the connective-tissue supporting substance there are both hard and soft adenomas; and in some examples spaces or cavities form, producing in advanced stages the large cysts of the subvariety designated as cystadenoma. The contents of such cavities and cysts vary considerably, being fluid, semifluid, or solid. There can be no doubt that some of these neoplasms produce the peculiar metabolic products of their glandular prototypes, although whether in the normal chemical and functional perfection is not yet known. For example, a fluid resembling bile is produced in hepatic adenomas, and colloid is formed in the alveoli of adenomas of the thyroid; and from clinical observations it



FIG. 59.—Tubular cystadenoma of the bile-ducts. $\times 35$.

seems that adenomas arising from adrenal rudiments give rise to the toxic products of the adrenal when it is functionally perverted.

Adenomas may arise in connection with any of the true glands or in the organs with a fibro-epithelial structure, and they appear not only in the substance of or in connection with pre-existing glandular organs, but often quite independently of them. Of the independent adenomas a great deal of interest is centered upon those which arise from secondary and displaced rudiments of the thyroid gland, and which reproduce quite typical thyroid structures in situations entirely outside of the normal location of the thyroid body; and in those cystic, solid, or papillomatous adenomas of the kidney or adjacent organs (the non-malignant hypernephromas) which have their origin in aberrant rudiments of the suprarenal gland.

The adenomas usually grow slowly, and rarely attain a great size. The tumors of the mucous surfaces and those in the liver, kidneys, testes, and

ovaries are often rapid in their growth, and may become quite massive. Cystic degeneration is not uncommon, especially in the new growths of the ovary, kidney, and testicle.

The encapsulated adenomas and the majority of those tumors appearing on free surfaces are of a benign nature. The papillomatous adenoma of the ovary or Fallopian tube may travel along adjacent peritoneal surfaces and produce disseminated growths. Other adenomas advance through lymph-spaces or tissue-spaces to considerable distances beyond the starting-point of the tumor. By breaking into blood-channels, adenomatous elements (for example, of thyroid adenoma) may be transported and reproduce their kind in distant localities, and this power of metastasis brings them closely in touch either with a variety of carcinoma (adenocarcinoma) or, in the case of hypernephromas, with sarcoma.

The development of adenomas from misplaced rudiments of the thyroid and adrenal glands furnishes one of the most convincing arguments for the embryonic theory of the origin of certain tumors, and no other explanation can be offered to account for such growths except that which ascribes them to proliferation of tissue-germs or rudiments of organs which have, in the course of development, been deposited out of their normal surroundings. Frequent demonstration of such aberrant organic rudiments of the thyroid gland and adrenal in adults, at the situations in which these tumors arise, makes this view reasonable. The adenomas are often also of congenital origin. In regard to adenomas in general, mechanic and irritative factors seem to play a predisposing role in some cases. A parasitic cause has also been suspected.

Cystomas.—We have already learned that a cystic metamorphosis, by which is meant the production of cavities, is an occurrence not uncommon in true tumors and in various degenerations. The adenomas are especially prone to this change, and that class of fibro-epithelial growths known as cystadenoma has many resemblances to the formations now to be discussed. Cystomas, cystic tumors, or cysts, as they are variously designated, may be defined as more or less spheric bodies, composed of a wall surrounding a cavity filled with fluid or semifluid contents. True cystoma is a new formation of cystic tissue (proliferation cysts). A large number of cystic new growths spring from misplaced embryonic rudiments, forming the cystic teratomas and dermoids.

The contents of the majority of true cystomas are fluid, resulting from the secretory activity of the lining cells or from transudation from blood and lymph-vessels. The fluid may take on a serous, mucoid, or colloid character; and cells in various kinds of retrograde change, like fatty and horny, may be present in the fluid. Further changes may take place in the cystic contents, resulting in the production of cholesterin, pigment, calcareous material, peculiar fatty products, and caseous material.

Closely related to retention cysts (page 117), though differing in origin, are the formations resulting from the persistence of fetal canals which normally become obliterated, and illustrated by cysts of the urachus, parovarium, spermatic cord, testicles (hydatids of Morgagni), and the suspensory ligament of the liver. Persistent or imperfectly closed fetal clefts may also give origin to cysts, as seen in the cystic hygromas of the neck in the former location of the branchial clefts.

As regards the proliferation cystomas, in some of them it becomes a difficult question to decide whether they should be regarded as cystomas in the

strict sense, or as fibro-epithelial tumors which have undergone cystic change. A common example of these cystomas is found in the ovaries, in which single, multiple, and compound (multilocular) cysts are found, often attaining large proportions. The ovarian cystomas are often complicated with papillomatous growths, generally projecting into the cavities, and are then called papillary ovarian cystomas. In a like manner the liver and kidneys may become the seat of single, multiple, and compound cysts, which sometimes attain a size sufficient to displace a part or the whole of the organ. The compound renal cystomas are generally of congenital origin, and aside from these the kidney may be occupied by single or multiple cysts, which recent studies indicate to have originated from misplaced remnants of the adrenals. Another organ in which cystomas are frequent is the mammary gland. Here, however, the new growth is often solid in parts which have an adenomatous structure, making a tumor which has been called adenocystoma; but single and compound cysts also appear here.

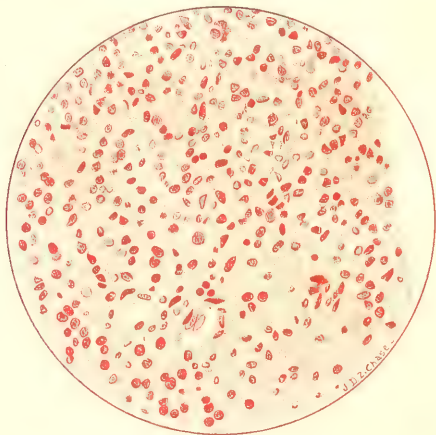


FIG. 60.—Glioma of the brain. $\times 335$.

Gliomas.—The central nervous system is the seat of a special kind of tumor—like itself, of ectodermic origin. These tumors are called gliomas, and have their beginning either in the elements composing the supporting tissue of the brain and spinal cord (the neuroglia) or from the cells lining their cavities (ependyma). In very rare instances real glioma may spring from the glia-layer of the retina. A great deal of confusion concerning the histogenesis of these tumors has been cleared up since the elaboration of specific stains for neuroglia (Weigert and Mallory) and for the nervous elements proper (Weigert, Pal, etc.).

The gliomas, while varying in size, rarely become massive; they may be single or multiple. Their color often resembles that of the surrounding nervous tissue, and their boundaries are rarely sharply defined, so that both a gross and a microscopic infiltration is found. Hard and soft varieties occur.

Microscopically either an extraordinary development of fibers with the special staining affinities of neuroglia, and few cells, or many cells and few fibers, are found. Incorporated in the substance of the tumor, in varying amounts, true nerve-tissue may be found, such as ganglion-cells and nerve-fibers. There is no positive evidence, however, that the nerve-cells and fibers proper proliferate in the tumor, so that such forms as "ganglionic neurogliomas" must at present be regarded as gliomas in which an unusual number of ganglion-cells and nerve-fibers have been included in the proliferating neuroglia, or as tumors in which ganglion-like cells without true nerve-branches are formed. Another point apparently settled by recent investigation is that in true gliomas mesodermic cell production does not predominate; hence the inaccuracy of such terms as "gliosarcoma." Furthermore, it now appears that most of the so-called gliomas originating in the retina, especially in young children, are in reality a form of round-cell sarcoma with pronounced metastatic tendencies, which glioma lacks.

While it has thus become possible to exclude certain neoplasms formerly classed with glioma, recent studies upon these tumors and upon neuroglia in general have given rise to other complications. The differentiation of true gliomatous tumors from other forms of pathologic neuroglial overgrowth, as seen in certain forms of sclerosis, of nodular gliosis, and of the central gliosis in syringomyelia, has become more difficult; indeed, it is not yet accomplished. The ependymal gliomas, the cellular elements of which have an epithelioid aspect similar to the normal cells lining the cavities of the central nervous system, in structure often simulate endotheliomas to a marked extent.

Upon a morphologic basis gliomas are classed into the richly cellular form (chiefly small, round glia-cells); the fibrillary form, with few cells and many well-developed neuroglia-fibers; the astrocytic or spider-celled; the spindle-celled; and the giant-celled varieties (Stroebe). The vascular supply of these growths is subject to wide variation. Some of the tumors are highly vascular, and it is not uncommon to find in them cavities of varying size filled with escaped blood, or cysts containing clear serous fluid from ancient hemorrhage. Such transformations as fatty and calcareous degeneration are sometimes seen, and an edematous and granular degeneration of the glia-cells also occurs.

We find both slowly and rapidly growing gliomas. They tend to infiltrate the substance of the brain and cord, but seem to respect such connective-tissue structures as the meningeal membranes, differing in this respect from sarcoma. They have no power of metastasis, unless we include with them the above-described doubtful tumors, retinal gliomas, which often give rise to secondary growths in such organs as the liver.

With the etiology of such pathologic affections of the brain and cord as disseminated sclerosis, nodular gliosis, and syringomyelia entirely obscure, and with our knowledge of normal neuroglia just in a phase of transformation, it is scarcely to be expected that much can be said upon the causation of glioma. An embryonic defect or aberration seems to be responsible for the origin of certain ependymal gliomas, especially the congenital ones. Traumatism is possibly a factor in some cases, and there is a growing suspicion that toxic or infectious agents will be found as essential causative influences, both in the various forms of gliosis and in the closely allied neoplasms, gliomas.

Neuroma.—This term has usually been applied loosely to all new growths containing nerve-cells or nerve-fibers in a fibromatous matrix, as, for example, amputation neuroma, multiple cutaneous and cirroid neuromas, which in a previous description we have properly looked upon only as fibromas of the peripheral nerves or of the ganglia, either of the cerebro-spinal or sympathetic system. Strictly speaking, a neuroma is a tumor composed of newly proliferated proper nerve-elements, either neurones or neuraxones, or both. It now appears that certain recently studied neoplasms can be included under this head.

Whether the so-called true neuromas of the spinal cord recently described (once in connection with syringomyelia, once in tabes, and again in an apparently normal cord, and in which there was an abundance of medullated fibers running promiscuously and having no apparent connection with the tracts of the cord) are real neoplasms or only artefacts, as Lubarsch suggests, is difficult to decide. But outside of the central nervous system some of the growths reported seem to fulfil all requirements, as, *e. g.*, the multiple dermal neuromas found by Knauss in young children. They contain both branching ganglion-cells resembling those of the sympathetic ganglia, and numerous medullated and nonmedullated fibers showing no anatomic connection with the nerves in the neighborhood, and apparently only to be explained on the basis of a proliferation of original nervous elements. Similarly the ganglionic neuromas show on careful histologic analysis with specific staining abundant ganglion-cells, apparently newly formed. These solitary ganglionic neuromas have been found in the thoracic, lumbar, hypogastric, and solar plexuses of the sympathetic, and also in the adrenal plexus.

THE SO-CALLED MALIGNANT TUMORS.

In the preceding discussion reference has several times been made to various properties of the so-called "malignant" tumors, and it now becomes our duty to study more in detail this very important class of neoplasms. They differ in their biologic activities, and especially in relation to their influences upon the host, from the so-called benign tumors. The term cancer is, in ordinary parlance, applied indiscriminately to all tumors which show the characteristics of malignancy; that is, to tumors the growth of which is unbounded and generally rapid, which tend to recur after operative removal, and which, above all, reproduce their kind in remote and often vital regions of the body, ultimately resulting in death of the patient. The malignant neoplasms are divided into two great groups, sarcoma and carcinoma, in each of which there are numerous varieties. We have already learned in the study of the preceding tumors that some of them may acquire certain of the properties of malignant tumors, like local recurrence, diffuse growth, and even the power of remote growth or metastasis, whereby they are brought closely in touch with the class of new growths now to be considered. In fact, the acquisition of one or more of the malignant characteristics in these otherwise benign tumor varieties is an occurrence which makes it very difficult to say just where the border-line is to be established between them and sarcoma and carcinoma.

It is generally customary to consider separately the two great varieties of malignant tumors, placing sarcoma at the end of the description of the connective-tissue varieties, and carcinoma after the fibro-epithelial tumors.

For the perfect types of sarcoma and carcinoma such a subdivision is quite appropriate, for no one would think of confusing a small round-celled sarcoma with a perfect adenocarcinoma. In the one case the mesodermic nature of the tumor-cells is plainly evident, and in the other the ectodermic or endodermic affinities of the proper tumor-cells are undoubted. In the intermediate subvarieties of sarcoma and carcinoma the difference is less striking, as seen in the case of the so-called alveolar sarcoma, or in the growths reproducing endothelial structures, or in those originating from the adrenals (malignant hypernephroma), in which the resemblance to certain forms of carcinoma is indeed striking, and in which it becomes exceedingly difficult to determine the histogenetic affinities. It is upon the morphologic basis solely that these two great varieties of malignant neoplasms have been differentiated, since in their life phenomena they have so much in common as to make a close distinction impossible.

That sarcoma and carcinoma do approach each other by easy gradients cannot be denied, and that there result a series of neoplasms, the place of which is upon the border-line between the two types, is also unquestionable. Perhaps it might be well to include them both under one head, as is done when the term "cancer" is used in its broad and popular sense. We must, however, look to the future to furnish us the only unassailable basis of classification for these as for all other true tumor varieties, viz., the etiologic one.

It is quite possible that we shall then find all the malignant neoplasms to possess a specific characteristic; but as our knowledge now stands, and for convenience of description, we must endeavor to recognize the morphologic distinctions of the perfect types of the two varieties, and consider them accordingly.

SARCOMA.

General Considerations.—Sarcoma is a malignant tumor of the connective-tissue type, the elements of which do not reach the morphologic perfection of mature and normal structures. The unfinished or embryonic condition of the tumor-elements, like that seen in developing mesodermic tissue or in granulation-tissue, has been looked upon as a peculiar feature of sarcoma. This definition is not sufficiently elastic, for there are subvarieties of sarcoma the elements of which do reach a high degree of morphologic perfection, and there are those in which the structure recalls more vividly epithelial than connective-tissue features.

Another differential point for separating sarcoma from carcinoma, upon which much stress has been laid, is the preponderance of the cellular elements over the intercellular substance in sarcoma, as compared with the relatively greater development of the framework or *stroma*, as it is called, in carcinoma. Here again careful study fails to emphasize this peculiarity, for many forms of sarcoma show a well-developed stroma in which a proper sarcoma body or "parenchyma" can be easily distinguished from the supporting framework or stroma.

Anatomic Features.—The gross anatomic features of sarcoma are by no means uniform. The size of the tumors differs according to the locality in which they appear and according to their peculiar structure. In the case of sarcomatous growths arising in connection with bone, it is not uncommon to find them attaining large size; while, on the other hand, the secondary foci of some varieties, especially pigmented or melanotic sarcoma, may be

so small as to appear dust-like, and may be diffused throughout an entire organ, or over a large area of free surface like the peritoneum. The original or primary growth is usually a single one, and the tendency is to assume a spheric shape; some, as chloroma and certain endotheliomas, grow as flat or plate-like masses. In the unpigmented forms the growth is either colorless or of a faint pinkish or grayish hue; but the highly vascular varieties are blood-tinged, while the pigmented forms may appear black, brown, bluish, green, or slate-colored. As compared with the average benign tumor, the consistency of sarcoma is soft, although examples are found with varying grades of hardness, culminating in growths with the consistency and nature of bone. The color and consistency of sarcomas may lack uniformity even in a single example, due to such factors as localized increase of blood-vessels, and hemorrhagic, fatty, mucoid, or other form of degeneration, sometimes even leading to the formation of cysts.

Histology and Histogenesis.—The data furnished by the histologic examination of sarcoma enable us to subdivide them according to the morphology of the tumor-cells. One large group has cells which uniformly tend to assume a spheric shape, giving the subvariety round-celled sarcoma; on the same basis the spindle-celled and the giant-celled forms may be differentiated; endothelioma and melanoma may be defined as distinct sub-varieties. The special morphology of these subvarieties will be separately discussed, but it is desirable to consider here some of the general histologic features of the sarcoma-cell.

In the attempt to demonstrate the specific nature of the sarcoma-cell, its various structural features have been successively reviewed, and some valuable acquisitions have been made to our knowledge of the cytology of tumors. In regard to the cytoplasm, it has been shown that the cytoplasmic constituents are subject to deviation in different varieties. In the spindle-celled, compact tumors the cytoplasm presents a distinct series of intracellular fibrils arranged to correspond with the long axis of the cell, with comparatively few and very small cell-granules. In richly cellular softer spindle-celled forms the fibrils are less pronounced and the granules better developed; while in giant-celled sarcoma and in many other well-developed forms scarcely a trace of fibrillary structure remains in the granular protoplasm. It would seem that the cells of the firmer and usually least malignant types attain nearest to the morphologic perfection of mature connective-tissue cells, while the more decidedly sarcomatous types fail to reach this stage.

It has been thought by some authorities that the poverty of nuclear chromatin was a specific characteristic of the sarcoma-cell, showing its reversion to the embryonic type; but more extended study fails to confirm this view, since all grades of chromatin production can be found in the nuclei of various sarcomas. The same consideration holds true for the nucleoli, of which there may be one or several. It is not uncommon to find massive sarcoma-cells with richly developed chromatin (hyperchromatosis), but even these have been found in other tumors and pathologic formations, and they appear to indicate stagnation or degeneration of the cell and nucleus. Some of the most marked examples of chromatolysis, or dispersion and solution of nuclear chromatin, are to be seen in certain richly cellular sarcomas, from the aggregation of the nuclear material into irregular masses to its breaking-up into dust-like particles and final disappearance. The dichromophilism of

the nucleolus and chromatin, by which is meant the different selective staining of these two structures in a mixture of anilin dyes (red and blue, for instance), while beautifully brought out in sarcoma-cells by the use of certain staining combinations, is not a distinctive attribute, being also observed in other cells.

The process of nuclear and cellular division in the sarcoma-cells proceeds both by regular and irregular methods. Karyokinesis or indirect segmentation is the rule, although it may deviate from the normal in various ways, and sarcoma-cells with asymmetric and pluripolar mitoses are frequently seen; although here again there is nothing that can be said to be peculiar to this variety of cell. Direct segmentation (amitosis) is a relatively frequent method of nuclear division.

Leukocytes, both of the polymorphonuclear and mononuclear forms, are present in varying amounts in sarcoma. Plasma-cells are frequently found at the border of the growing tumor, and mast-cells may also be seen. The function of the leukocytes is not entirely clear, though they are known to gather not only in the tissue-spaces and blood-vessels of the intercellular tissue, but also to invade the proper tumor-cells. They are especially abundant about necrotic foci, and the most reasonable interpretation of their presence is to ascribe to them the role of phagocytes, engaged in disposing of the degenerated products resulting from the breaking-up of the nuclear chromatin and the death of the cell. Distinct purulent foci are occasionally found, and are probably the result of a bacterial infection of the sarcomatous tissue.

The disposition of the denser spindle-celled subvarieties of sarcoma is to grow slowly, and often to produce a rough capsule by which they are separated from the mother-tissue. Such tumors may grow for months and years with little evidence of malignancy, but their true nature is often shown when, after some traumatism or other irritating influence, they suddenly grow rapidly, and sometimes give rise to an extensive crop of secondary deposits. Even the more rapidly growing and destructive types may become arrested and remain latent for a varying period, when they unexpectedly assume malignant properties. For the most part, the richly cellular forms grow with great rapidity.

Metastasis.—The sarcomas possess the capacity of metastasis. This function is not a universal one in them, however, for some varieties never reproduce new growths outside of their primary abode—in this respect differing from carcinoma, which more uniformly tends to metastatic reproduction. Still, this occurrence is often seen in sarcoma, especially in the richly cellular and rapidly growing varieties, and at times the vast number of secondary growths which originate from a primary focus is almost beyond belief. The secondary deposits may appear in such mesodermic structures as the subcutaneous tissue, fascia, bones, and muscles; or in the viscera, like the liver and lungs. In general, the secondary tumors reproduce the typical structures of the primary growth. Dissemination of the elements giving rise to metastases, while more often taking place by the blood-vascular system, is not limited to it, for the lymph-channels may also serve as the pathway of transportation.

Blood-vessels.—While an abundant development of blood-vessels is a common occurrence in sarcoma, this feature is liable to considerable variation. The blood-vessels in the stroma may be histologically perfect, they may be simply distended tubes bounded by a single layer of endothelial

cells, and in some instances even this endothelial layer seems to be absent, and the blood coursing through channels bounded solely by the tumor-cells. In the highly vascular forms, free hemorrhage into the tumor-substance is often seen. Other forms of degeneration, like fatty, mucoid, hyaline, and cheesy, are not uncommon; and certain substances giving the microchemic reactions of amyloid or glycogen are at times present.

Age.—Sarcoma is especially the malignant tumor of childhood and young adult life, differing in this respect from carcinoma, which commonly appears after the fortieth year. It may, however, occur at any age.

Sites.—The usual sites are the fascia, subcutaneous tissue, muscles, bones, articular cartilage, meningeal membranes, and more rarely the viscera, like the kidneys, liver, and lungs. The tumor may also grow in pigmented and unpigmented birthmarks or nevi, either of a blood-vascular or lymph-vascular structure. It is as though these transformed foci, already on the way toward mesodermic tumor-growth, furnished an especially favorable soil for a sarcomatous proliferation. Sarcomas often occur in places exposed to traumatism, at the seats of scars or of irritation from pressure and inflammation. But in addition to the nevi, the scars, and the areas of traumatism, there must be something more to result in the production of a sarcoma, for only a few of these defective localities become the seats of such tumors; and besides this, it must be remembered that sarcoma more often appears in situations in which no such previous changes have occurred. The underlying factor is apparently as far from being definitely answered in the case of sarcoma as with tumors in general.

Etiology.—Of all the theories advanced in the study of this problem, however, the one which ascribes to a parasitic influence the exciting agency in sarcoma seems best to meet the conditions of our present knowledge. There is so much in common between sarcoma and certain lesions resulting from known infectious agents, the infective granulomas, that we are justified in the hope of ultimately finding parasitic agents here as well. Of the investigations, that centered upon the blastomycetic fungi seems now to be most promising, since the presence of particular yeast species has been demonstrated in sarcomatous tumors, and by cultural methods these organisms have been isolated in purity, and by comparative inoculation experiments they have been found to produce new growths. None of them, however, could on rigid histologic analysis be pronounced sarcoma.

The Varieties of Sarcoma.—**Spindle-celled Sarcoma.**—One of the most common sarcomas is that made up of more or less elongated or spindle-shaped cells—the so-called spindle-cell sarcoma.

The tumors vary in size and tend to assume a globular shape, especially when their growth is unconfined. The new growth is generally white or only slightly tinged with color. Both hard and soft kinds are found. Their growth is usually slow in the case of the denser masses, and more rapid in that of the soft ones. Often an imperfect outer fibrous layer separates the tumor from the structures bounding it; this is particularly the case in the hard tumors. On macroscopic sections the surface may be uniform, or it may be broken by islands of an osseous nature, by spicules of bone, or by masses of calcareous substance. Foci of softening or of degeneration are not uncommon. The primary growth is usually found in the localities in which spindle-celled connective tissue pre-exists.

There is no rule about the metastasis of this variety, for some of the

growths pursue an essentially benign course, while others have all the attributes of malignancy.

Microscopically it is possible to distinguish differences in the size of the tumor-cells, enabling us to differentiate large and small spindle-celled sarcoma; in the amount of intercellular substance, which, when abundant and distinctly fibrillary, gives the so-called fibrosarcoma, or, when the seat of mucoid metamorphosis, the myxosarcoma; and in the abundance of blood-vessels. Osseous or osteoid tissue is occasionally present, giving rise to the osteosarcoma or osteoid sarcoma.

A very ready method of studying these tumors is in fresh-teased preparations, in which the individual cells can be observed. It will be found that in the soft and richly cellular forms the cells are usually much elongated, and taper to delicate end-processes, and that the proper tumor-substance is made



FIG. 61.—Spindle-celled sarcoma of the choroid. $\times 135$.

up of these elements closely set, and with very little, if any, supporting substance between. Very frequently these cells dispose themselves parallel to the blood-vessels, as though choosing their walls as a support; but at other times the cells may arrange themselves in lines of growth that show no evident preference for the direction of the blood-channels. In the small-celled tumors, the elements are quite uniform in size and appearance; while in those with large cells, variability in shape—polymorphism—is more marked, and it is not uncommon to find a mixture of spindle-shaped, oval, and round cells of varying size. The nuclei are ovoid in the small-celled forms, and provided either with a small amount of chromatin, making a poorly defined network, or with a compact mass filling the nucleus; but in the large cells the nucleus may exhibit a well-formed and abundant chromatin framework with one or more nucleoli. The nucleus may be irregular in outline, and even subdivided into numerous accessory nuclei, producing a multinuclear or

giant cell. Both normal and abnormal segmentation and fragmentation of the nucleus are seen.

The newly formed blood-vessels of the tumor proper generally develop poorly, and scarcely reach a more mature stage than that seen in young granulation-tissue; *i. e.*, an endothelial tube surrounded by the tumor-cells. When well-formed arteries and veins are found, they can, for the most part, be regarded as pre-existent vessels of the matrix.

Spindle-celled sarcomas of periosteal origin often reproduce an imperfect kind of bone, in which the tumor-cells are found lying in anastomosing spaces where bone-corpuscles normally exist, and in which the ground-substance is more or less homogeneous and the seat of calcareous deposit. Those spindle-celled tumors in which calcification occurs in the ground-substance are called osteosarcomas; those in which the ground-substance

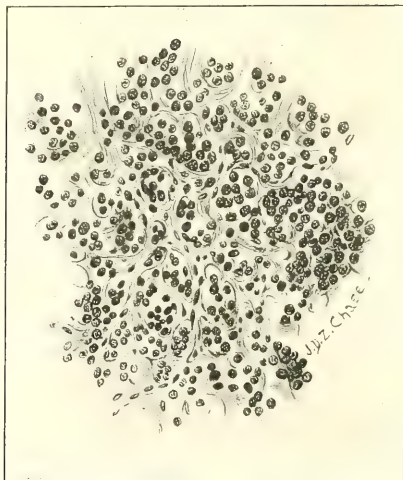


FIG. 62.—Round-celled sarcoma. $\times 200$.

takes the aspect of bone, but in which calcification fails, are distinguished as osteoid sarcomas.

Round-celled Sarcoma.—This is a sarcoma composed of small round cells. It grows more rapidly, and is generally softer and more malignant than the spindle-cell sarcoma. It is found in the same localities, and also occurs in the testicle and kidney.

There is a large-celled and a small-celled form of round-celled sarcoma; in the large-celled examples, polymorphous elements with oval, spindle-shaped, and irregular forms are not uncommon. Considerable difference in the amount of intercellular substance is found, some small-celled tumors being composed almost wholly of closely packed cells, with but a trace of intermediate supporting substance, while in others a distinct stroma can be made out. The rule is, however, for the intercellular substance in these

neoplasms never to reach the advanced stage found in the harder example of spindle-celled sarcoma (fibrosarcoma). In one form of large round-

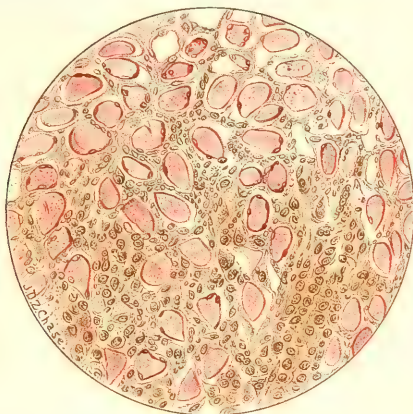


FIG. 63.—Round-celled sarcoma invading muscular tissue. $\times 300$.

celled sarcoma the tumor-elements take on the aspect of epithelial cells (epithelioid or endothelioid), and these cells arrange themselves in well-

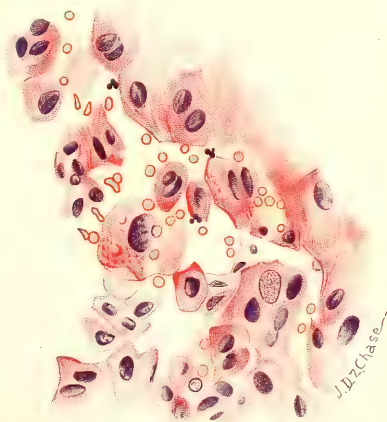


FIG. 64.—Large round-celled sarcoma. $\times 500$.

localized groups, separated from each other by a distinct stroma. These are the *alveolar sarcomas* described long ago by Billroth, and it is such forms

that give rise to the confusion concerning the sharp demarcation of sarcoma and carcinoma. These alveolar sarcomas may be of endothelial origin, belonging to the endotheliomas.



FIG. 65.—Alveolar sarcoma. $\times 35$.

In some of the round-celled sarcomas there is a distinct reticulum resembling that of lymphadenoid tissue ; such tumors are called lymphosarcomas.

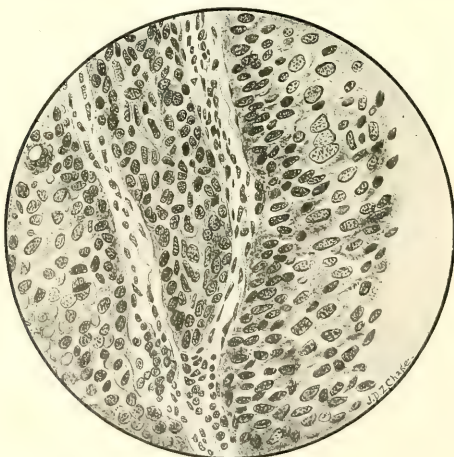


FIG. 66.—Alveolar sarcoma. $\times 335$.

They occur most frequently in lymph-glands and the spleen, also in the pituitary body.

Giant-celled Sarcoma.—While multinuclear cells are not uncommon in

the large-celled examples of both spindle-celled and round-celled sarcoma, there is a class of sarcomatous growths in which giant cells are uniformly found in such numbers as to give a characteristic stamp to the tumors. This is not to say that the multinuclear cells are the sole tumor-elements, for besides them we find both spindle-shaped and round cells; the giant cells are simply uniform morphologic features of the new growth, and are present in considerable numbers. Giant-celled sarcoma is also called myeloid sarcoma or myeloma.

The typical neoplasm of this variety is the growth arising in connection with the inferior maxillary bone, especially of children, making one of the forms of epulis, malignant epulis. It is not apt to give to metastasis, while other giant-celled sarcomas not rarely do so.



FIG. 67.—Giant-celled sarcoma. $\times 135$.

Most of the giant-celled sarcomas arise in connection with the osseous system, either from the periosteum or from the bone-marrow, but they have been found in the mammary and thyroid glands.

The tumor is composed of round or spindle-shaped cells of varying size arranged about the giant cells, which are large protoplasmic bodies containing many nuclei, not rarely one or more clear vacuoles. There is, as a rule, very little stroma in these growths. The giant cells vary in shape, sometimes having an unbroken circular or oval outline in section, again being decidedly irregular, with the outline broken by offshoots or protoplasmic processes extending in various directions. Their nuclei are sometimes small and extraordinarily numerous, even reaching hundreds in a single cell; other times they are larger, more liberally supplied with chromatin, and not so numerous; while in still other examples a massive nucleus with little evidence of subdivision is seen. Often the nuclei are gathered at one pole of the cell, leaving a clear protoplasmic field at the opposite side,

just as is seen in the giant cell of tubercle. Various inclusions may be found in the substance of the giant cells. The giant cells are usually surrounded by a clear space of varying width, probably as the result of shrinking in the process of hardening the tissue.

The methods by which this remarkable subdivision of the nucleus is brought about are, for the most part, direct segmentation and fragmentation, although some cells show the nuclear figures of karyokinesis, usually in the stages of pluripolar or asymmetric division.

The origin of these peculiar multinuclear cells is an interesting problem. There can be little doubt from recent studies that some of them are to be regarded as phagocytes, the function of which is to remove various foreign substances, an assumption which is strengthened by finding masses of blood-pigment, of hyaline, amyloid, or glycogenic material in their interior. Perhaps some of the cells arise by confluence of smaller ameboid endothelial cells, as has been suggested in explanation of the origin of other giant cells, and as would appear possible from the peculiar protoplasmic offshoots sometimes seen in these giant cells.

Melanotic Sarcoma ; Melanosarcoma ; Melanoma.—This is a pigmented sarcoma, the pigment being melanin.

The naked-eye appearances are usually most striking. The tumor varies in size and shape and is generally soft and friable, but can be distinguished readily by its pronounced color, which in the ordinary example varies from a dead black to a grayish hue. The shade of color varies not only in different tumors, but often in different parts of the same tumor, for portions quite colorless may lie close beside those which are as black as coal. The vascular supply of the tumor is sometimes very rich, and areas of hemorrhage are at times found. In some of the secondary melanomas, particularly those encountered in the liver, a peculiar liquefaction of some of the tumor-masses may take place, probably the result of a diffuse necrosis.

The primary seats of the melanotic sarcoma are especially such regions as normally contain pigment, like the skin and the choroidal layer of the eye. The tumors have a marked tendency to grow in areas of the skin the seat of birthmarks, the pigmented nevi or moles. Melanomas are also found in viscera and in connection with bones, and are either periosteal or medullary in origin ; but it is quite doubtful if, in these instances, the primary tumor (perhaps exceedingly small) growing from a pigmented region has not been overlooked, so that these osseous and visceral tumors are really metastases.

From the histologic standpoint it is possible to distinguish two kinds of melanotic sarcomas : those with spindle-cells and those in which the cells are epithelioid in morphology and in which a stroma separates them into groups or alveoli, like alveolar sarcoma. The spindle-celled tumors originate especially in the choroid of the eye, and reproduce these elements in their secondary growths, which attack the liver by preference. The skin is usually the seat of the alveolar melanotic sarcomas, and the tumors growing from nevi are apt to follow this type. Unna makes a strong argument for the epidermic origin of cutaneous melanomas springing from pigmented nevi ; while Ribbert regards them as arising from mesodermic pigmented cells (chromatophores). Recent investigations seem to corroborate the view of Unna. Round cells and giant cells may be found in the melanotic tumors of bone.

The pigment appears in dust-like particles, in larger granules, and some-

times in good-sized masses. The individual granules are highly refractive and of a yellowish tinge, so that they are readily seen either in fresh preparations or in stained sections. The deposit of pigment shows microscopic as well as macroscopic variations. In the alveolar growths the tendency for the granules is to collect in certain cells at the periphery of the cell-groups, near the stroma in which the blood-vessels lie, or even in clusters about the blood-vessels, due probably to the amoeboid movement of the chromatophores or pigment-cells. In the choroidal tumors the pigment is more uniformly deposited in all the cells. In some secondary growths, more especially those in the liver from the choroid, the pigmentation may be so intense as to cover the cells and make it almost impossible to recognize them in microscopic sections; here also a further step leading to the liquefaction above noted is taken, when the cells die and leave only a granular protoplasmic detritus mixed with an abundance of pigment-granules. The pigment is often carried away from the tumor. Some of the cells in both cutaneous and choroidal melanoma possess several processes, one or more of which extend to a considerable distance as a tube-like prolongation containing pigment-granules and strongly resembling chromatophores (Depuë).

As regards the nature and source of the pigment in these tumors, much doubt still exists. It was at one time supposed that it was derived from the blood-coloring matter, but this is very questionable, especially as it is rare to find this substance giving the usual iron reaction of blood-pigment. Careful chemical analyses have been made of it, and while observers are not agreed upon certain fundamental points, especially as to the presence of iron, it seems to be established that the pigment contains a considerable proportion of sulphur. It is probable that the chemical nature of the substance differs in tumors originating from different localities, and that it is a product of the chemical activities of the tumor-cells themselves.

Chloroma.—Another pigmented tumor with some resemblance to the small-celled sarcoma usually known as lymphosarcoma is the quite rare and very remarkable chloroma. This, which is characterized by a peculiar greenish color, originates for the most part in connection with the bones (skull, vertebra, and humerus), generally in intimate relationship with the periosteum. The tumors have been found in lymphatic glands, in the liver, kidneys, and in the marrow of the bones, as metastatic growths. In connection with the bones they usually form flat, plate-like masses, often extending over large areas. The color is light green, dark green, grayish, or even yellowish, being most intense when the tumor is first removed from the body, and fading on exposure to the air or in various preservative solutions.

Histologically chloroma is composed of round cells resembling the small or large lymphocytes, with a delicate reticulum, strongly resembling the appearance of lymphoma. The pigment is not pronounced in sections of hardened tissue, but can be made out best in sections of the fresh tumor or in freshly teased preparations, when it appears in the form of highly refractive granules within the tumor-elements. The chemical nature of this coloring matter is still obscure, though there is reason for believing that it is in some way combined with fat, of which the cytoplasmic granules seem to be composed. The tumors are well supplied with blood-vessels.

The weight of opinion at present concerning the nature of chloroma is to regard it as a disease of the lymphadenoid system, showing certain affinities with leukemia and pseudoleukemia. The clinical course, while closely resem-

bling that of malignant lymphoma or lymphosarcoma, is in some respects different. These neoplasms belong to the class of sarcomatous new growths, for which a parasitic cause will perhaps ultimately be discovered.

Endothelioma.—This subvariety of sarcomatous tumors has gradually become defined, although many points relating to it are still in dispute. The present tendency is to include among the endotheliomas many of such anomalous forms of sarcoma as angiosarcoma (Fig. 69), psammoma, myxosarcoma, perithelioma, and cylindroma.

The endotheliomas are separated from other sarcomas on histogenetic and morphologic grounds. They include all those tumors arising from endothelial cells, no matter how they may subsequently be transformed. Thus it is evident that the endothelium of the blood-vessels and of the perivascular lymph-spaces, of the lymph-vessels, and of the great serous cavities (peri-

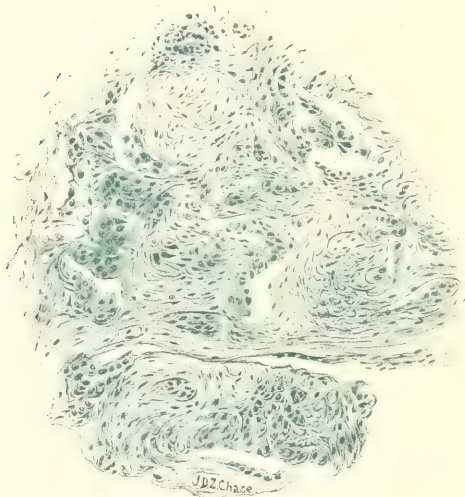


FIG. 68.—Endothelioma of the pleura. $\times 145$.

toneum, pleura, meninges) may furnish the elements of these neoplasms. When the close morphologic resemblance between endothelial and epithelial elements is recalled, it can be readily understood why endothelioma and carcinoma are often confused; and there is the additional fact that, even in such matters as the amount and disposition of the stroma, no essential histologic difference can be shown between some of the examples of these two tumor varieties.

The essential tumor-element is the round, flat, or cubic endothelial cell, often called, from its resemblance to epithelium, "epithelioid." Depending on the particular structure from which the first proliferation takes place, the tumor-elements arrange themselves in various ways. In those of blood-vascular (endovascular) origin the cords of tumor-cells often proceed in lines

strongly recalling the original vascular network, and in some of the recent stages it is possible to describe the thickened endothelium, the remains of the proper vessel-wall, and even to find blood-elements in the lumen of the proliferating endothelium, this lumen remaining more or less evident in the mass of endothelial cells or becoming obliterated. In endotheliomas of lympho-vascular origin, essentially the same appearance is found. When the growth departs from the endothelium of the lymph-spaces of the tissues, a more pronounced alveolar structure is produced, with anastomosing cords and nests of epithelioid cells surrounded by a well-defined connective-tissue stroma, with more irregular lines of growth than are seen in the other types. Depending upon the nature and amount of this stroma, the alveolar endothelioma presents examples with but little ground-substance of a finely fibrillar character, intermediate types with well-defined stroma, and others

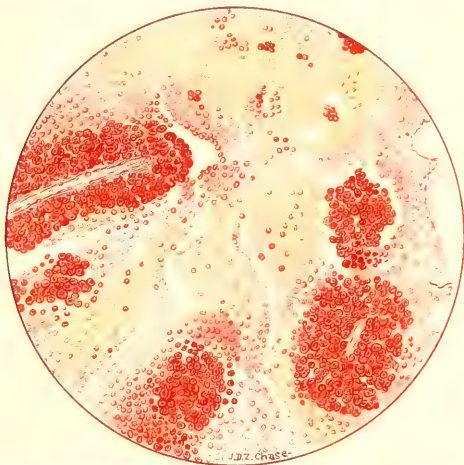


FIG. 69.—Plexiform angiosarcoma of the eye. Extensive areas of degeneration infiltrated with blood are seen between the sarcoma-cylinders. $\times 135$.

with abundant coarse, fibrous supporting tissue crowding the endothelial cells into narrow communicating clefts or causing them to disappear.

The stroma of some endotheliomas is subject to metamorphoses of various kinds. A myxomatous alteration produces the kind of tumor often called a *myxosarcoma*. In another variety, usually originating from the blood-vascular endothelium, a hyaline transformation of the vessel-walls and of the stroma produces the peculiar growths called sarcomatous *cylindromas*.

The dense endotheliomas of the dura represent endothelial new growths in which the stroma has become densely fibrous, and in these tumors spheric calcareous concretions of a laminated structure are often found, apparently identical with the so-called "brain-sand" normally present in the meninges and pineal gland; hence they are called *psammomas* or "brain-sand" tumors. In older tumors of this character the dense stroma has often so overgrown the endothelial elements as to make their recognition difficult; but in

newly developed psammomas a distinct endotheliomatous structure can be made out.

Certain members of this variety of sarcomatous tumors grow very slowly, show little or no tendency to invade surrounding structures, and rarely if ever produce secondary growths; this benign form of endothelioma is exemplified in the dural psammoma. On the other hand, there are endotheliomas which grow very rapidly, forming large primary tumors which encroach upon

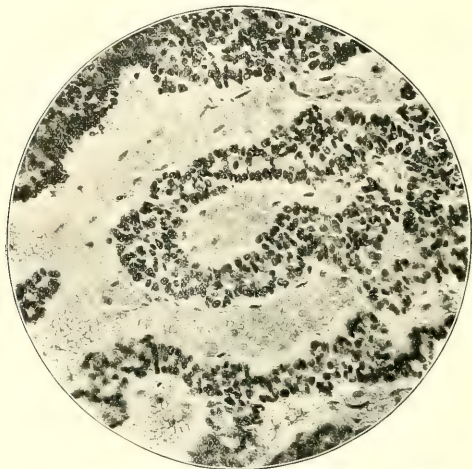


FIG. 70.—Endothelioma of the dura mater. $\times 200$ (Karg and Schmorl).

the surrounding tissues, and which reproduce their kind in metastatic growths in various regions of the body.

Occasionally a pronounced phagocytosis is observed in some of the sarcomas, the process being carried on by the tumor-cells themselves or by large macrophages.

CARCINOMA.

General Considerations.—We are now confronted with a large and important group of new growths springing, for the most part, from elements of ectodermic or endodermic origin; although it is generally accepted that tumors of this variety may arise from the cells of such organs as the kidneys and the sexual glands, organs which are of purely mesodermic origin. The parenchymatous elements of these tumors are of epithelial derivation, springing from the pavement-cells lining the cutaneous and mucous surfaces, from the cylindric cells covering large areas of mucosa, or from the cells making the acini of glandular organs and lining their ducts. It has already been stated that the fibro-epithelial neoplasms may approach the confines of carcinoma. In a way, a carcinoma can be regarded as a papilloma or an adenoma which has “gone bad”; that is, has acquired properties which impel it to break through its surroundings and to grow in a way that

departs from the tendency shown by the benign fibro-epithelial tumors. For example, an adenoma of the breast reproduces with some morphologic fidelity the normal glandular acini; a carcinoma of this same region fails to produce so perfect a structure. Hence it is that the carcinomas have often been designated as "atypical" fibro-epithelial neoplasms. Here, as elsewhere in the domain of biology, it is not an abrupt step which leads from the one to the other species—there is always an intermediate ground on which the widely divergent types are brought together; and thus it happens that there are papillomas and adenomas which assume more and more of an atypical growth until they must be regarded as carcinomas, and there are carcinomas the structure of which is so orderly as to resemble that of an innocent fibro-epithelial growth. We are still ignorant of the influence of such factors as heredity, environment, the mechanics of cell growth and proliferation, and the exciting causes which must play the same parts in relation to the pathologic formations known as tumors that they do elsewhere in biology; and, with no well-established laws to guide us, we grope in the dark when attempting to account for the variations, just as the zoologists once did with respect to animal species.

Manner of Growth.—The carcinomas which grow from free surfaces generally tend to take on a papillomatous or villous aspect, producing the so-called "cauliflower growths." Sometimes the surface growths are roughly nodular, again they are mere thickenings of a flat surface. In the substance of organs, a more pronounced tendency to nodular growth is shown. The beginning of a carcinoma—in such a locality as the lip, for instance—is usually indicated only by an ill-defined thickening and hardening, and even in the advanced tumor this failure to be sharply demarked from the bounding tissues is usually shown. The same infiltrating tendency characterizes most of the growths of visceral origin, so that it is often impossible for the eye to separate the normal from the abnormal tissue, and even the microscope shows islands of tumor-cells far beyond the apparent boundaries of the growth. It is as though the tumor-elements were poured into the tissues in a molten state, and, by virtue of their fluid condition, permeated in all directions the spaces and clefts existing naturally in the tissues. The direction of growth or infiltration is modified by the character of the tissues bounding the carcinoma. In such structures as are soft and loose-meshed the outlying boundaries are more extensive than is the case when dense membranes or osseous or cartilaginous structures are encountered by the growing tumor. A very curious spectacle is often presented in the attempt of these growths to overcome cartilaginous or bony obstacles, in that they grow against them and produce a pressure necrosis, instead of invading them directly, while at the same time availing themselves of every possible channel presented by softer portions to advance by infiltration. In this way extensive and irregular tumor-masses are produced, and in advanced growths it is not uncommon to see all the structures in a given region of the body, as the neck, for instance, bound into one great diseased mass, the cement being composed of carcinomatous tissue growing in every direction. Petersen has recently studied the growth of carcinoma by the method of plastic reconstruction, and finds two types of growth: one in which the tumor grows from a single center, sending out processes in various directions, and one in which the growth springs from multiple centers.

Another phenomenon especially characterizing these neoplasms when

growing from free surfaces is necrosis of their superficial portions, resulting in ulceration or erosion. After the main tumor-mass dies and liquefies, it leaves a ragged and dirty ulcer, at the edges of which is a thickened ring. The necrotic processes are attended with the formation of pus, of false membrane, and of various kinds of fluid or solid detritus, and the development of putrefaction, often with most repulsive odors.

General Characteristics.—There is nothing about the color of carcinomatous neoplasms that serves to distinguish them from other tumors. That same whitish, grayish, or pinkish hue noted in so many other tumors is observed in them. There are certain cancers¹ that exhibit pigmentary deposits. When growing into fatty tissue, the islands of cancerous new growth can sometimes be easily detected with ordinary vision on account of a peculiar pearly luster which contrasts sharply with the yellow fat.

While there is really no limit to the size attained by the tumors of this variety, they do not, as a rule, become very large—principally, no doubt, because from their baneful influences the patient fails to live the necessary time. But good-sized masses are often found; and in other cases, especially when metastases are formed, the tumors may be extraordinarily numerous, causing an enormous enlargement of the affected organ.

Both soft and hard carcinomas are found, the difference depending for the most part upon the proportion of parenchyma and stroma. The very soft, richly cellular examples of glandular origin have often been called “medullary” or “encephaloid” cancers from their brain-like consistency, while the harder variety with well-developed fibrous ground-substance is called “scirrhus” cancer or scirrhus. The consistency of individual tumors is also influenced by various degenerations and metamorphoses to which carcinoma is subject.

The vascular supply which finds its way to the tumor by the stroma varies in amount; some are highly vascular tumors, and some have comparatively few blood-vessels and lymph-channels. The soft tumors may be so well supplied with blood and lymph that they yield a fluid on slight pressure or upon scraping the cut surface; and this fluid, or “cancer-juice,” as it is styled, is composed of tumor-elements mixed with blood-cells and lymphatic corpuscles. The lymph-trunks leading from a rapidly growing cancer may become enormously dilated, and on incision yield a cancer-juice.

Sites.—Primary tumors have the following habitats, given in their order of frequency (Birch-Hirschfeld): The uterus (especially the vaginal portion); the external skin (lower lip, more seldom the lobe of the ear, eyelids, cheek, and extremities); the female mammæ (much more rarely the male breast); the stomach (pyloric region, more rarely the cardiac end, and most rarely the fundus); the rectum; the esophagus; the ovaries; the testicles and epididymis; the external genitals (glans penis, scrotum, clitoris, labia, and vagina); the prostate and the urinary bladder; the pancreas (especially its head); the kidneys; the intestinal mucosa; the thyroid; the bile-ducts (and gall-bladder); the liver; and the bronchi. The secondary growths are found especially in the lymph-glands, lungs, peritoneum, pleura, spleen, kidneys, and the osseous system.

Metastasis.—The malignancy of carcinoma is shown by its infiltrative local growth, whereby offshoots insinuate themselves in all directions into the substance of the parent tissue, choosing the regions of least resistance

¹ The term cancer is here used as synonymous with carcinoma and the German “*Krebs*.”

for its most pronounced growth. It is this faculty that makes the operative removal of these tumors so hopeless, for outside of the reach of the surgeon's knife there is usually an island of cancerous tissue which causes a recurrence after the excision.

Again, the function of colonization or metastasis reaches its highest degree in cancer, and adds the finishing touch to its malignant attributes. The transportation of the tumor-elements, by which remote secondary carcinomas are produced, is especially effected through the lymphatic channels. Very often the march of the new colonies can be traced by following the anatomic distribution of the lymphatics and their glands. The group of lymph-glands nearest the primary tumor interposes the first barrier, and itself becomes cancerous; from here new and more remote glands become

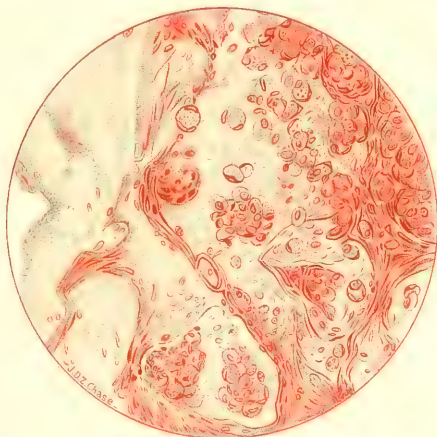


FIG. 71.—Cancer of the rectum. Mucoid degeneration in the stroma and epithelial cells. $\times 200$.

affected, and finally the viscera are reached. Much less frequently carcinoma uses the blood-vessels as routes for its metastases. This is generally brought about by the penetration, into a vessel, of a sprout of carcinomatous growth, forming a foreign body or a thrombus in the lumen of the vessel, from which minute particles or single cells are carried into the blood-stream as cancerous emboli, to lodge in other parts of the body. In this way it sometimes happens that an extraordinary number of these tumor-germs are sent into the circulation, producing an acute and widespread infection of other regions (acute carcinosis). It is not uncommon for these emboli to be detected in the capillaries on careful microscopic examination of such organs as the liver and lungs, even before they have reproduced extravascular growths. The destructive effect of such an ever-extending growth as carcinoma upon normal organs and tissues is readily comprehended. There is practically a substitution of a growing mass of foreign and functionally useless tissue for the normal structure; more than this, such a mass of cancerous growth is more easily subject to

degeneration, to necrosis, and to infection than the normal structures which it invades, and thus imperils them. Then, too, there is reason to believe that these abnormal growths have the capacity of elaborating their own harmful products (cytotoxins) as the result of their biologic activities, and that these products exert a baneful influence both upon the structures immediately surrounding the carcinoma and, by absorption, upon the body at large.

To say, however, that all carcinomas are functionally impotent is not correct; for there is an undoubted tendency for these neoplasms, when originating in certain important glandular organs, to partake, even if only in an imperfect manner, of the physiologic attributes of the parent tissue. Thus it appears that carcinomas of the adrenal, of the pancreas, and of the thyroid, even when extensive and for the most part displacing the normal glandular substance, do not cause in the victim those peculiar auto-intoxications which result from the destruction of these organs from other causes; from which we can only conclude that the elaboration of their peculiar products has been taken up by the cells of the invading new growth.

Parenchyma and Stroma.—When approached from the standpoint of its minute morphology, one feature of carcinoma stands out boldly: that is, it is a new growth composed of two essential parts—a *tumor-parenchyma* proper, and a supporting framework or *stroma*; one consisting of epithelial-like cells of various kinds and combinations, the other consisting mostly of a connective-tissue substance carrying within itself the vascular channels of the new growth.

Looking in general to the parenchyma of carcinoma, and in particular to the cells composing it, a very important question presents itself: Is there anything so peculiar in the morphology of the cancer-cell that it can be looked upon as a *specific element*? That is, is the cancer-cell to be distinguished morphologically from the normal epithelial cell, or from the epithelial cell in which other morbid processes are at work? This query has already been touched upon in the General Introduction to Tumors (page 161), and has been answered in the negative; here we shall repeat it and answer it similarly, though entering a little more into details.

Recalling again the assertion that many carcinomas resemble in their morphology such fibro-epithelial neoplasms as papilloma and adenoma, and extending this likeness to the constituent cellular elements, as may in all propriety be done, we can comprehend that there are carcinomatous cells which resemble ordinary epithelial cells so closely that no morphologic analysis which our present facilities for examination afford enables us to say that the individual cell came from a normal epithelial structure, from an adenoma, or from a carcinoma. Which is to say, in other words, that those cancers most closely approaching the morphology of typic neoplasms show no specific cellular features. However, in many rapidly growing cancers the constituent cells show alterations which, if not peculiar to these tumors alone, are nevertheless most conspicuous in them. The cell may often attain a size which is rarely reached by other morbid epithelial cells. Its protoplasm may show changes in the disposition of the cytoplasmic reticulum and in the cytoplasmic granules. Its protoplasm may be vacuolated in a pronounced degree, or it may contain certain peculiar spheric or ovoid bodies with special affinity for certain dyes, or it may contain masses of pigmented, hyaline, colloid, keratogenic, or glycogenic material; and other inclusions,

like engulfed neighboring cancer-cells, or leukocytes, or foreign débris, may also be found. We have already seen that the cells of sarcoma exhibit many of these peculiarities. Turning to the nucleus, the most marked anomalies are found. Nuclei excessively large are seen, sometimes beside those below the usual size. The chromatin may be scanty (hypochromatosis) or excessive (hyperchromatosis), and it may be arranged in a loose mesh-work or aggregated in a compact mass. Nucleoli are single or multiple and sometimes excessively large. As in the case of sarcoma, the nucleoli and chromatin reticulum of the nucleus exhibit a marked dichromophilism, but this is in no way specific for carcinoma.

The figures produced by nuclear division in carcinoma show all the various abnormal types to which reference has already been made. Irregular and pluripolar mitotic figures have been looked upon as especially significant of cells of carcinomatous origin; and though they are occasionally seen in epithelial cells engaged in rapid regeneration or under the influence of certain infections, they certainly furnish the most important diagnostic element in determining the nature of a neoplasm from its cells alone. With ever-improving methods and with further search, it may be that some cytologic feature will be discovered which will stamp the carcinomatous cell as an individualistic morbid element.

But it is only by the grouping of the constituent cells, and by the relation of these cellular colonies to their stroma, and the relation of the whole newly formed tissue to its environment, that carcinoma can positively be differentiated. To this subject of cell disposition we shall refer in more detail when considering the separate varieties of carcinoma.

The stroma in which the carcinomatous cell groups are disposed is usually a more or less perfect connective tissue, sometimes closely resembling that seen in nonmalignant fibro-epithelial tumors, and again exhibiting certain distinctive features. There is a wide variation in the stage of organization reached by the stroma in different carcinomas and in different parts of the same tumor. A richly cellular growth, with scanty development of intercellular fibrils resembling embryonic connective tissue or that seen in regeneration of this tissue, is found with particular frequency in the rapidly growing neoplasms. In other instances the organization is more perfect, the stromatic cells becoming spindle-shaped with more and more intercellular substance, reaching finally a stage in which dense connective tissue with quiescent cells is found between the islands of cancer-cells. As naturally would be supposed, the softer neoplasms are those with poorly developed stroma.

Along with the proper connective cells, the stroma of carcinoma often contains other elements. Many foci of embryonic mesodermic cells or lymphoid cells are found, making the familiar "round-celled infiltration" of these tumors. Leukocytes, both the polymorphonuclear and mononuclear forms, are seen in the tumor-framework; and the different tinctorial varieties of the white blood-cell—the neutrophile, acidophile, and basophile—are represented. Plasma-cells, often in large numbers, appear in the tumor-stroma, marking inflammatory reactions; and mast-cells sometimes appear, especially at the growing borders of the tumor, where retrogressive changes are going on in the matrix. Occasionally giant cells are seen in the stroma, apparently in the act of phagocytosis; and various foreign substances, like cholesterol crystals and detritus, are found in them. Bodies

with unusual staining reactions are also at times present, of a class represented by the peculiar spheric fuchsinophilous granules described as "Russell's fuchsin bodies." Bacteria, and perhaps yeast organisms, are to be found; and in rare cases in which a tuberculous infection is implanted upon a cancer, tubercles are encountered in the stroma, along with their bacilli.

Both blood-channels and lymphatic channels abound in the stroma, which thus serves as the carrier of these structures; the number and disposition of these nutrient canals vary in different tumors.

A very important peculiarity of carcinoma is *its ability to utilize surrounding tissue-elements as a supporting framework for its own cells*. Invading a part in which connective tissue pre-exists, the groups of cancer-cells simply utilize this tissue as a stroma; and what happens in the case of connective tissue also occurs in other structures. For instance, the cells of fatty tissue or the fibers of striated or nonstriated muscle may be called upon to furnish the cancerous framework; and, especially in the case of metastatic growths, the adenoid cells and reticulum of lymph-glands or the columns of liver-cells may supply the supporting framework for the new growth. For the most part the nuclei of the stroma show amitotic division, but it is also possible to discover various figures of mitotic division here.

Retrogressive Changes.—Evidences of degeneration are not uncommon in the cancerous stroma. A fatty metamorphosis is sometimes seen and may affect wide areas of the growth. A hyaline transformation is also possible, the transformed stroma taking on a homogeneous, glassy, swollen aspect, while its cells become indistinct. Closely allied to the preceding are the mucoid, colloid, and gelatinous degenerations in the stroma, and in rare instances the altered stroma has been found to give an amyloid reaction. Calcification, even in carcinoma having no connection with bones, is observed, the calcareous material being mostly deposited in the form of concentric masses, though cases have been noted in which a general deposit of lime salts took place at the periphery of a carcinoma, making a sort of calcareous capsule for the tumor.

Certain of these degenerations affect both the tumor-parenchyma and the stroma; at other times only one of the basic structures becomes involved. Several varieties of carcinoma have been established on this ground. That variety in which the stroma has taken on abundant growth to an advanced stage, resulting in the contraction and even death of certain groups of carcinomatous cells, and producing a growth often of stony hardness, is the "scirrhus cancer." A richness in cells, as has before been noted, together with a scanty or loose-meshed and usually abundantly cellular stroma, characterizes the "medullary" or "encephaloid" cancer. A colloid or gelatinous degeneration of the parenchyma, with or without a similar change in the stroma, producing a growth in which the tumor-elements are surrounded by a mass of the foreign material, makes the "colloid cancer," and similarly a mucoid transformation would give rise to the growth designated as "myxomatous cancer." Hyaline metamorphosis of either or both the parenchyma and stroma, upon becoming extensive, makes a growth resembling the cylindromatous sarcoma, and is therefore styled "cylindromatous" carcinoma.

Histogenesis.—Turning our attention now to the question of the histogenesis of carcinoma, we are largely prepared, from what has preceded, to ignore the older theories which ascribed the origin of the tumor-elements to a

metaplasia of connective-tissue cells,¹ and to accept the doctrine propounded a quarter of a century ago by Thiersch and Waldeyer, that *cancer-cells originate in altered pre-existing epithelial cells*. Numerous observations have settled this point, apparently beyond dispute, especially the studies upon young carcinomas in various localities. In the skin, for example, a direct continuity may be traced between the carcinomatous foci and the sprouts of pavement epithelium, which in the diseased area plunge more deeply into the underlying connective tissue than is normal. At some particular point the pavement epithelial cells assume an undue activity, multiplying rapidly and producing cell groups which push their way into the regions beneath. That the cells found in cutaneous cancers originate from those of the pavement epithelium is clearly shown by their retention of many of the biologic characteristics of the parent tissue; for they take the shape and general appearance of the mother-cells, often reproduce such structures as the protoplasmic bridges of epithelial prickles, and undergo various keratogenous changes seen in their progenitors. In the same way, cancers of the stomach and intestine reproduce the cylindric epithelium of the original surface or glandular epithelium; those in the bronchi spring from the cylindric cells of the mucosa, in the lungs from the flat cells lining the alveoli, and in the liver from the original liver-cells. The direct transformation of the normal to the abnormal elements has been repeatedly witnessed by competent observers. There are, however, some apparent contradictions to these views of carcinomatous histogenesis, as seen in the case of flat-celled neoplasms originating in the digestive mucosa, in which only cylindric cells normally are found; but the phenomenon is explained by assuming a metaplasia of the normal epithelial elements preceding the growth of the carcinoma, an assumption strengthened by the evidences of a similar metaplasia under other conditions. For those rare instances in which a primary carcinoma begins in a purely mesodermic structure, like bone, a previous embryonic misplacement of epithelial elements seems the only satisfactory explanation.

The conduct of the connective tissue which becomes the stroma of the beginning carcinoma is not always easily followed. Whether an activity and proliferation of its cells precede or succeed the primary epithelial growth is a question upon which opinions differ. It is held on one side that the connective-tissue elements first arouse into activity, sending wandering cells between the epithelial cells of a given part, by which these latter elements become separated from their original continuity and then begin to exhibit those increased and peculiar proliferative properties common to carcinomatous cells. A great deal of weight is laid upon this severance of the epithelial cell from its natural abode, as a potent factor in the histogenesis of carcinoma, though it is evident that the cell must contain within itself a capacity for reproducing carcinomatous offspring, else any epithelial cell or group of cells thrown out of normal surroundings by such factors as mal-development or traumatism might make a cancer, which of course is not the case. So far as the participation of connective-tissue proliferation is concerned, it may be, as has been claimed, that its activity and growth are a prominent factor in the histogenesis of some carcinomas; but in other instances

¹ In this connection it must, however, be recalled that the opinions of embryologists concerning the immutability of the germ-layers are not so positive as formerly; and that certain experimental pathologists claim that a metaplasia of epithelium into connective tissue can occur. If this be true, the converse also may be possible—that is, metaplasia of connective tissue into epithelium.

it seems to play a decidedly secondary part, not assuming noticeable proportions until the epithelial growth has attained a considerable extent; and finally it is in point to recall those cases in which the growing carcinoma appropriates for its stroma other elements besides connective tissue.

Etiology.—Turning first to the patient, we are met with the fact that cancer is pre-eminently the malignant neoplasm of advanced life. Statistics gathered with great care from large numbers of cases show that 70 per cent. of these neoplasms appear between the fortieth and seventieth years of life, and that below the fifteenth year the disease is practically unknown.

There must be something, then, in the environment afforded by the tissues of advanced life that makes an especially suitable soil for cancer, or there must be at this time in life an action of causes not operative earlier. As to the causes themselves, we must distinguish sharply the predisposing from the exciting factors. Of the first we know considerable from clinical statistics, but of the latter we are still much in the dark.

The theory of embryonic misplacement, once vigorously espoused in connection with carcinoma, now finds little support. The characteristic tendency of cancer to start as a primary growth in such localities as the lips, nipples, anus, and uterine neck, where mucous and cutaneous surfaces or flat-celled and cylindric-celled surfaces adjoin, was held in support of the embryonic hypothesis; for here, it was argued, where germ-layers once met, misplacement of rudimentary tissue-germs would be especially liable to occur. But it may properly be asked why *carcinoma* should be the favorite neoplasm to appear in these situations, and again it must not be forgotten that these same localities are especially exposed to traumatism and to infection.

Irritation, both immediate and continued, has a profound influence in determining the localization of carcinoma, unless all clinical evidence on this head be set aside. A trustworthy history of traumatism in the site selected by the primary carcinoma has been obtained in a fair percentage of cases. The origin of these malignant growths in scars resulting from traumatism or from ulceration bears on this point. Chronic irritation, doubtless for the most part of an inflammatory character, predisposes to carcinoma in individuals reaching the cancer period of life, as shown in the appearance of these growths in the gall-bladder or bile-ducts in cases of biliary calculus and accompanying chronic inflammation. The origin of carcinoma in mammary glands once the seat of mastitis is to be similarly interpreted, as is also the case when the disease appears in the cervix of a uterus long subject to irritating discharge and slow inflammation. The notorious predilection of cancer for the lips and tongue of tobacco and alcohol users can likewise be charged to previous irritation. In many of these cases there is, at the commencement of the irritation, an infection of the site from which the cancer starts, and the inflammation is due to the continued action of infectious organisms and their toxic products. This tendency for certain infections to prepare a soil for carcinoma is well shown in the cases in which the disease arises in connection with lupus, and probably also where cancer originates in partly healed gastric ulcers. In all of these instances, however, only one factor in the causation of the neoplasm has been considered; otherwise there would be no accounting for the well-known facts that, after all, comparatively few of these seats of irritation become cancerous, and that this disease frequently originates where there is no evidence of previous irritation. There must be a *specific exciting factor* among the primary causative

influences ; and here we reach the realm where speculation begins and is most prolific.

The problem of the etiology of carcinoma is very much like that pertaining to sarcoma ; and at the present time the *parasitic theory* of its etiology claims the greatest share of attention, though it meets with opposition from some of the most accomplished students of this subject. Both in the discussion of the etiology of tumors in general and in connection with sarcoma, the points in favor of the parasitic theory were mentioned, and they apply to carcinoma as well. Granting the existence of a minute animal or vegetable parasite which invades certain epithelial cells and incites them to the abnormal proliferative activity resulting in the cancerous neoplasm, many aspects of the problems concerning these tumors are made clear, though there now seem to be insurmountable obstacles in other directions. The appearance of cancer at the various orifices of the body and in localities subjected to traumatism and to irritation of various kinds would support the parasitic theory, for in all of these places especially favorable openings for infection or soils with lowered resistance would be offered. The carrying over of the specific parasite in the transported cells would make more easy the explanation of carcinomatous metastases. That parasites do exist in carcinomatous tumors no one can deny, and that representatives of bacteria and yeast fungi have been here found is unquestionable. But to prove the specific causative relationship of any of these microscopic species is quite another matter, and certainly has not been accomplished at the present time. On the other hand, we find the views of distinguished investigators who attempt to explain the etiology of carcinoma on other grounds to be entirely out of accord with each other, and it must therefore be said that at present this important problem is still unsolved.

Varieties of Carcinoma.—The subdivision of carcinoma seems to be best accomplished on purely histogenetic grounds, and accordingly it is appropriate to classify the varieties into (*a*) the pavement-celled, (*b*) the cylindric-celled, and (*c*) the glandular.

Pavement-celled Carcinoma.—Flat or pavement-celled carcinoma originates, for the most part, from similar cells lining the cutaneous or mucous surfaces of the body. The quite familiar neoplasm growing from the lip, and often styled an *epithelioma*, represents the type of these tumors. They begin as undefined infiltrations or thickenings of a part, and may grow beneath the surface for considerable areas, or spring above the surface in the form of nodular or wart-like growths, sometimes taking a villous or cauliflower-like appearance. They are generally more firm than cancers growing within the body cavities or organs, and some of them become very dense and horn-like. Necrosis of the central portion of the growth may set in early, producing ulcerating cancers.

Depending upon the shape assumed by the tumor-mass, neoplasms of this class have been described as “warty” cancers, “villous” cancers, and “horny” cancers.

This variety of carcinoma may appear in the skin of any region of the body, but chooses with especial frequency the various orifices, like the lips, nostrils, eyelids, prepuce, vulva ; and in the pavement-celled mucous membranes it may also appear, selecting especially the tongue, esophagus, larynx, vagina, and vaginal portion of the uterus.

The microscopic anatomy of these cancers exhibits a tumor-parenchyma

composed of flat, round, or polygonal cells, varying in size and arranged in groups or alveoli, surrounded by a stroma more or less rich in cells. In the newly developing portions of the growth the parenchymatous cells are mostly round and undifferentiated, while the stroma is abundantly cellular with an imperfect development of fibers. In more advanced portions the epithelial cells tend to become flattened and to exhibit various metamorphoses like the keratogenous or horny changes to which pavement epithelium is subject. Here the alveoli become much larger, and in the central portions marked degenerative changes, even resulting in death of the cancer-cells, may be seen, while at the periphery young cells occur with evidences of nuclear activity in the shape of regular or irregular forms of mitosis. There is no uniformity in the shape assumed by the colonies of cancer-cells; in the newer portions of the growth they tend to advance in straight lines, several cells lying side by side, following in regular order those in advance, and invading the lymph-spaces of the tissue; while in the older groups a central area can be seen, from which offshoots extend in all directions, often anastomosing freely with other groups. The histogenetic impress of pavement epithelium is marked in various ways upon the older portions of the cancer-parenchyma, and shows with especial prominence in the frequent reproduction of the intercellular protoplasmic bridges or "prickles" which pass through the cement-substance between the cells, making a very perfect picture of the "prickle-cells" as seen in normal surface epithelium. Eleidin and keratin granules also appear in the more mature cells, and a peculiarity of many of these superficial cancers is the production of concentric whorls of cells more or less advanced in horny changes and exhibiting a repugnance to nuclear stains, constituting the so-called "epithelial pearls" or "birds' nests" of flat-celled cancer. In these concentric bodies may be found some of the most marked evidences of nuclear and protoplasmic necrosis in various stages, together with the peculiar process of inclusion of one epithelial cell by another, and an active invasion of leukocytes, some of which are degenerated and others apparently engaged as scavengers to devour the detritus resulting from necrotic processes.

In the older portions of these tumors the stroma may attain a coarsely fibrous character like old scar-tissue, thus becoming an important element in producing the dense and hard flat-celled carcinoma. In other growths, or in certain regions in a single tumor, the stroma is more cellular and the fibrils less numerous, until a condition like that of embryonic or regenerating connective tissue appears. Scattered in various localities in the stroma, foci of small-celled infiltration are found, and, especially about the growing edge of the neoplasm, collections of plasma-cells and mast-cells appear.

Cylindric-celled Carcinoma.—These neoplasms may arise either from the cylindric cells covering such mucous surfaces as the digestive tract and respiratory passages, or preferably from the cells lining tubular glands like those in the intestine, and from the ducts of acinous glands like those of the mamma, which are lined with cylindric cells. They are most often found in the stomach (forming a portion of the gastric carcinomas), the intestines, rectum, bile-ducts, and uterus, and begin as localized infiltrations, rapidly involving the structures lying beneath the mucosa, frequently ulcerating in their central portions. For the most part, the tumors are soft and they tend to degenerate, especially in the direction of colloid and mucoid meta-

morphoses. Growing from a free surface, they often produce papillary or villous neoplasms.

The parenchyma of these carcinomas shows the cylindric cells, generally closely resembling those normally encountered, arranged in lines of growth that produce more or less perfect tubules. That is to say, the cells, several layers deep, arrange themselves around a central space, and in some portions of the new growth the resemblance to normal tubules may be quite perfect. As the tumor advances, however, the normal limits of tubular growth are disregarded and the cylindric-celled tubular sprouts extend in all directions, while the excessive proliferation of their cells may alter the shape of the original lumen of the tubule or even close it entirely. In

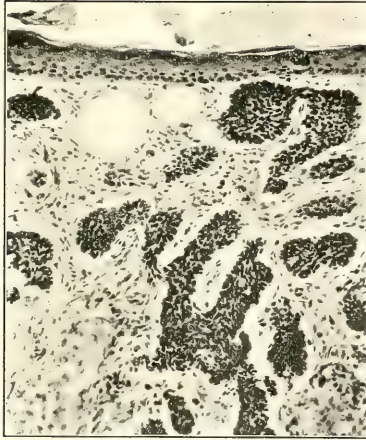


FIG. 72.—Tubular carcinoma from the forehead. $\times 150$. (Dr. Montgomery's case. Dr. Rickett's preparation.)

rapidly growing tumors, many of the cells composing the abnormal tubules contain nuclei in the process of mitosis.

The stroma of cylindric-celled carcinoma is generally more cellular in well-developed portions of the tumor than is the case in flat-celled cancer, and this cellular connective tissue is more regularly disposed about the parenchymatous elements. In studying these neoplasms, especially from a diagnostic point of view, it is important to note the relative position of the proliferating tubules. When these are found growing into and beneath the muscularis mucosa in the intestine and stomach, for instance, no doubt need be entertained as to the nature of the neoplasm (Ribbert).

Glandular Carcinoma.—This takes its origin from the glandular epithelium of such organs as the mamma, pancreas, liver, thyroid, salivary glands, kidneys, prostate, testicle, and ovaries. Like the preceding group, the glandular carcinomas begin as infiltrative growths in the parent tissue, and for the most part produce rather soft tumors. The histogenesis of these cancers and their microscopic morphology are such as to produce a more or less

marked resemblance to the original glandular structure; hence the propriety of the term *adenocarcinoma*, often applied to them. In the discussion of the fibro-epithelial tumor known as adenoma, attention was invited to the occasional difficulty of drawing a sharp line between the benign and the cancerous glandular growths. The macroscopic details upon which this differentiation depends are mainly the infiltrative and lawless tendencies of the primary cancerous growth, features which are strongly emphasized by its minute anatomy.

Histologically the glandular carcinoma exhibits a parenchyma composed of polymorphous cells arranged in alveoli which often anastomose widely and are separated by a connective-tissue stroma. The type of this subvariety is seen in the cancer of the breast arising from the lacteal glands. The polymorphism of the epithelial cells is well shown in specimens



FIG. 73.—Adenocarcinoma of the rectum. $\times 65$.

obtained by scraping the tumor-surface and freshly examined. Their nuclei are usually well developed and often multiple, producing carcinomatous giant cells; karyokinetic figures, both of normal and abnormal types, are abundant in the soft and rapidly growing examples, and inclusions appear frequently. A common alteration of the parenchymatous cells is fatty degeneration. The alveoli vary widely in their size and in the grouping of the cells, but the predominant characteristic which serves as the most important diagnostic point is the atypical arrangement of the cell groups of the alveoli as compared with the normal gland and with simple adenoma. The lumen of the normal gland is generally lost, and the absence of the *membrana propria* and of the normal ducts is an important diagnostic feature.

The stroma of these tumors shows the usual variations common to other cancers.

PLACENTOMA.

Within the last few years we have specific knowledge of a peculiar kind of tumor which has so unusual an origin and exhibits such a distinctive morphology and physiology that it can only be considered separately. It is a *malignant neoplasm* in the fullest sense of the word, exhibiting the morbid physiologic characteristics of sarcoma or carcinoma.

No doubt, before its individuality was discovered, it was confounded with uterine sarcoma or carcinoma, and, even since it has been recognized, a great deal of doubt has been entertained as to its origin, as shown with great clearness in the various terms which have been employed to describe it, as, for instance : *Deciduoma* and *Deciduoma malignum*, *Sarcoma choriondeciduocellulare*, *Sarcoma chorii*, *Sarcoma choriocellulare*, *Choriocarcinoma*, *Carcinoma syncytiale*, *Epithelioma seriotinale*, and *Synectioma malignum*. It is evident that this terminology refers mostly to the ideas which have been held concerning the histogenesis of these tumors, and this applies to the term *Placentoma* here adopted, which is at least noncommittal to certain of the theories.

Placentoma has been found primarily in the cavity of the uterus and the Fallopian tubes, but not in ovarian and abdominal pregnancies. Here it springs from the placental site (*decidua serotina*), either during the course of a uterine or tubal pregnancy or after the termination of this pregnancy (at term or prematurely), from placental remnants at the site of the decidua serotina. It is notable that placentomas follow not only apparently normal gestation, but with especial frequency (about one-half of the cases) such an abnormal form as mole-pregnancy. More remarkable still are the cases reported by Schmorl and by Harris, in which no primary neoplasm was found in the uterus or Fallopian tubes, but in a distant organ like the kidney.

The tumors grow as soft, spongy, villous, bleeding masses of varying size, sometimes single and again as multiple nodules springing from the chosen area. In appearance they are not unlike portions of placenta, and detached pieces removed from the uterus have several times been at first mistaken for retained placenta. They generally grow with great rapidity, causing the uterus to increase in size quickly and progressively, while, from their highly developed blood-supply and fragile consistency, hemorrhages often accompany their progress. They have no respect for adjacent tissues, and invade the uterine wall much as a carcinoma would. More than this, they are capable of producing metastatic growths which appear in such regions as the vagina, labia, lungs, kidneys, gall-bladder, thyroid, intestines, and even in the brain. The secondary nodules resemble placenta, and are generally not large. They may be very numerous in the lungs, giving an appearance like disseminated miliary tubercles.

The clinical picture which placentoma produces is briefly as follows : After the termination of a full-term pregnancy, after an abortion, or after the expulsion of a mole, generally with a very short interval, uterine hemorrhage starts afresh, while at the same time the uterus begins to swell. From the loss of blood, and doubtless also from the intoxication peculiar to malignant tumors, the patient rapidly becomes anemic and develops a peculiar cachexia. Shreds and pieces of the new growth may be passed from the uterus, and an examination reveals the spongy, friable mass filling the uterine cavity. Secondary tumors soon appear, their presence being visible when they attack

the vagina or labia, or shown by physical signs and the spitting of blood when the lungs are invaded. After a very short time (three to nine months) the patient succumbs to the devastating disease. In the cases with no uterine tumor, persistent nausea and rapid decline have been noted.

The histology of placentoma is characteristic, and its peculiar features have been plainly shown by Marchand, to whom our present knowledge upon this point and upon histogenesis is mostly due. The tumor is made up of *parenchyma alone*, the absence of a newly formed integral *stroma* being one of its histologic characteristics; which, while very striking, is not confined to this neoplasm alone, as we have seen in the description of carcinoma (page 208), which sometimes utilizes as a framework the structures in which it grows. The parenchyma consists of two chief portions: an extensive

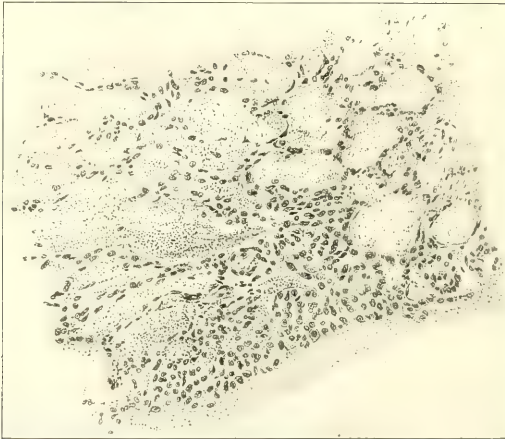


FIG. 74.—Section from primary uterine tumor, showing its alveolar structure with the cavities filled with blood; $\times 60$ (Williams).

protoplasmic ground-substance, *syncytium* or *plasmodium*, usually arranging itself into a sort of network to produce an alveolar structure, and of numerous small polyhedral cells, which group themselves in the alveoli provided by the peculiar disposition of the plasmodium. In the most typical form of placentoma there is no evidence of a subdivision of the plasmodial network into separate cells, though it contains numerous nuclei; but in other cases the protoplasmic network does divide into irregular nucleated masses, into giant cells, and into immense epithelioid cells with large nuclei richly endowed with chromatin. Vacuoles are often abundant in the syncytial tissue, and it not infrequently shows evidence of hyaline metamorphosis. The smaller, polyhedral, generally mononuclear cells are remarkable for the frequency with which they show glycogen granules. Along with these two chief parenchymatous elements, the tumor-substance contains abundant blood-sinuses with areas of free hemorrhage, and detached masses of syncytium or syncytial cells are often found floating in the blood-sinuses. As a result of

these hemorrhages, a copious deposit of blood-pigment, especially in phagocytic cells in and around the tumor-parenchyma, can be seen.

As to the origin of the tumor-parenchyma, much discussion has been aroused, it being commonly held, prior to Marchand's studies, that the elements were of a decidual nature—that is, were developed from the decidual cells of the maternal decidua, these being originally of connective-tissue birth; hence the term "sarcoma," applied to these growths. Marchand's views, now commonly accepted, are that the tumor-parenchyma originates exclusively from the two epithelial layers covering the chorionic villi which project into the maternal decidua at the site of the placenta (*decidua serotina*). Of these two epithelial coverings of the chorionic villi, the external one (*syncytium*) is supposed to be of uterine origin from the epithelium of the uterine or tubal mucosa (and glands), and furnishes the plasmodium of the syncytial neoplasm; while the inner layer (Langhans's layer) is of fetal origin (ectodermic cells), and furnishes the small polyhedral cells contained in the alveoli of the placentoma or syncytionoma.¹

The transportation of the tumor-elements by which the secondary growths are produced is effected almost entirely through the venous channels, either through the parenchymatous elements (especially the plasmodial masses) of the primary tumor breaking (or eroding) into a blood-vessel, or through the detached particles floating in the blood-sinuses. The lymph-spaces of the uterine wall are not infrequently invaded by the tumor-cells, but the rarity with which the pelvic lymph-glands are infected speaks against the spread of the neoplasm through these channels. Thrombi containing syncytial masses are especially frequent in the pulmonary blood-vessels; and parietal lodgement and penetration of the vessel-wall may be seen, though whether this is due to the ameboid movement of the plasmodium or to its digestive action (which, like certain carcinomatous cell groups, or like the implanted impregnated ovum, it seems to possess), or to both, is not fully determined.

As to the etiology of these neoplasms of so remarkable an origin, nothing whatever is known.

TERATOMA.

It remains for us briefly to consider still another class of new growths which stand in close relation to several varieties of the tumors already discussed. These are the *teratomas*, a group of neoplasms containing heterogeneous tissue-elements usually so far advanced in development as plainly to resemble some one or more of the mature tissues or organs, either in macroscopic or microscopic morphology or both. The dermal structures in one kind of teratoma (*dermoid*) plainly recall the skin and its component parts, while skin, muscle, cartilage, bone, intestines, certain viscera, nervous tissue and the like are reproduced in the more complicated teratomas with more or less anatomic fidelity. Sometimes the reproduction is so complete that the teratoid tumors contain plainly recognizable fetal parts, the confines of that

¹ Whether the syncytium is really of maternal or fetal derivation can scarcely be regarded as settled at the present time, but in either case there seems to be no doubt as to its *epithelial nature*; and, with the ectodermic nature of the other elements of the placentomatous parenchyma proved, there can be no doubt as to the epithelial affinities of this neoplasm. Therefore, if there is any propriety at all in attempting to classify it with other tumors, it most naturally falls in with carcinoma.

group of pathologic anomalies known as congenital malformations being reached. Indeed, it seems that teratoma serves to bridge the gap between a number of what we are pleased to style "true" tumors and the malformations only to be ascribed to errors of embryonic or fetal development, and for this reason the embryonic theory of tumor-genesis here obtains important support.

Usually these teratoid growths are not large, though examples weighing twenty or thirty pounds have been recorded. As a rule, the tumor-mass is not characteristic in appearance, but at times even the external configuration recalls some imperfectly formed bodily part. Cystic metamorphosis, as has already been remarked, is extremely common, and these generally epithelial-clad cavities contain fluid (clear or cloudy), gelatinous, mucoid, fatty, grumous, or calcareous material. A soft, wax-like substance, white or yellowish, containing cholesterol crystals, exfoliated epithelial cells and scales, and hairs, is frequently found, more especially in the so-called "dermoids" of the ovaries. Teeth, more or less perfect, and nails are quite common objects in the walls of dermoids; and skull-bones, separate or united in anatomic relationship, imperfect limbs, eyes, brains, bowels, etc., have all been recognized at times, the latter three for the most part only on microscopic section. It is here noteworthy that Wilms found nervous tissues in traces or larger amounts in ordinary ovarian dermoids, and it is highly probable that similar careful histologic analysis in all teratomas will reveal a more complex organization than is at first apparent. Thorough microscopic study should be made not only of tumors whose teratoid structure is clear, but also of those neoplasms in which anomalous tissues appear as muscle in the kidneys or testicles, cartilage in the mammary glands, and so on, since these growths seem only ascribable to embryonic aberrations and often show more structural complexity than would be suspected from a superficial examination.

The ovaries are the favorite point of origin of teratomas, the testicles being less often involved. Outside of the genital glands, teratoid growths may spring from the abdominal cavity, from behind the peritoneum, in the kidneys, the mammary glands, parotid gland, about the eyeball, in the neck especially at the points where the gill-clefts once existed, and in the brain; that is to say, in situations where important embryonic foldings occurred. Many cutaneous cysts (like the so-called "atheromatous cysts") are of a teratoid nature, though they also may start from postnatal causes, like traumatism and operative procedures, which produce mechanic transplantation of cutaneous structures.

Most teratomas grow slowly, but some of them increase rapidly in size, even rivalling sarcoma and carcinoma; and these rapidly growing teratoid neoplasms show other evidences of malignancy, like spreading along contiguous surfaces, recurrence after removal, and even by metastasis, whereby new tumors, with a portion or all the structural complexity of the original, spring into existence in remote localities. We see, therefore, that even in this class of tumors, whose embryonic origin is usually so easily demonstrable, the same morphologic and functional characteristics of tumors proper exist.

As to the period of life in which these tumors occur, it is really strange to find an exception to their appearance as congenital growths, though this is occasionally the case, for teratoma has been found to begin its growth even in adults. Here we have another argument for Cohnheim's embryonal

theory, holding that tumors arise from misplaced embryonic rudiments, which may remain latent for years.

It will be inappropriate to discuss here all the theories advanced to account for this group of new growths. The perfect teratomas which reproduce fetal parts most faithfully must be regarded as instances of fetal inclusion (the *fœtus in fœtu* of Meckel); and in their production such factors are probably concerned as accidents to the ovum in its early segmentations (demonstrated as worthy of consideration by modern experimental teratology), or subsequent faulty fissions in the young embryo. The included embryo or embryonic part must remain dormant in those cases in which complex teratoid growths appear after birth, a condition difficult to comprehend. Probably in the less complex teratomas, a pinching-off of tissue-rudiments, such as Klebs suggests, is what actually happens during development to furnish the teratoid nidus.

PATHOGENIC MICROPARASITES.¹

INTRODUCTION AND GENERAL MICROPARASITOLOGY.

IN its whole aspect, pathology has been changed in the quarter-century now ending. This change, which is sufficiently far-reaching to be termed a revolution, is to be ascribed to the discovery of the pathogenic microparasites and of their intimate relationship to disease. The description of many morbid processes has been entirely rewritten in this period, which, from the marvellous progress made, must be regarded as one of the great epochs in human advancement. Light has been thrown on many of the obscure problems in pathology, and there is daily evidence of further achievement in this new field. So that now, to understand the nature of many a given disease, the student must be familiar not only with its morbid anatomy and

¹ Since it is now customary to present the subject of bacteriology in the medical curriculum as a course separate from and usually preceding pathology, it seems superfluous to go into elementary descriptive details in this section of a text-book on pathology or to encumber it with technic minutie. More profit appears attainable by assuming that the student, in approaching this topic, comes with a theoretic and practical knowledge of elementary bacteriology. For those who take up this section without the preliminary knowledge just indicated, a study of one of the standard text-books on bacteriology now readily accessible is advised, either as a preparatory course or as a supplement to the various topics here presented. Laboratory practice is, however, indispensable; it alone gives tangibility to the knowledge of parasitology gained from a study of such text-books and of this article.

Having particularly in mind the needs of the student, it has been thought wise not to encumber this section with bibliographic references. Those who would seek the original sources of information should consult the special journals devoted to parasitology, such as the *Centralblatt für Bakteriologie, Parasitenkunde und Infektionskrankheiten*, *Archiv für Hygiene, Zeitschrift für Hygiene und Infektionskrankheiten*, *Annales de l'Institut Pasteur, Hygienische Rundschau, Arbeiten aus dem kaiserlichen Gesundheitsamte*; and those dealing with pathology and bacteriology, such as *Virchow's Archiv, Centralblatt für allgemeine Pathologie und pathologische Anatomie, Beiträge zur allgemeinen Pathologie und zur pathologischen Anatomie, Archives de Médecine expérimentale et d'Anatomie pathologique, Journal of Pathology and Bacteriology, and Journal of Experimental Medicine*. For studying the literature, besides the general indices, such reviews as *Baumgarten's Jahresbericht über die Fortschritte in der Lehre von der pathogenen Mikroorganismen*, and the *Ergebnisse der allgemeinen Pathologie und der pathologischen Anatomie* of Lubarsch and Ostertag are especially valuable.

Among the manuals and text-books, Flügge's *Die Mikroorganismen* on general bacteriology, Migula's *System der Bakterien* and Fischer's *Vorlesungen über Bakterien* on the systematic side, are rich in information, and the first two provide extensive bibliographies.

Bacteriology as applied to clinical studies is best represented by Heim's *Lehrbuch der Bakteriologischen Untersuchung und Diagnostik*, and by Levy and Klemperer's *Clinical Bacteriology*. Mention must also be made of Duclaux's *Traité de Microbiologie*; the section on Parasitic Fission-fungi, Yeasts, Moulds, in Ziegler's *Lehrbuch der allgemeinen Pathologie und pathologischen Anatomie*; the sections on Infection and Pathogenic Microbes by Charrin, Charrin and Hugounenq, and by Roux in *Bouchard's Traité de Pathologie Générale*; and Flexner's article on Micro-organisms in the *Twentieth Century Practice of Medicine*. Gautier's *Les Toxines Microbiennes et Animales*, and Vaughan and Novy's *Plasmains and Leukomains* deal especially with the chemistry of the poisonous bacterial products. Among the more general and elementary works are Lehmann and Neumann's *Bakteriologische Diagnostik*, Abel's *Taschenbuch für den bakteriologischen Praktikanten*, Abbott's *Principles of Bacteriology*, Schürmayer's *Pathogene Spaltpilze*, Sternberg's *Text-book of Bacteriology*, McFarland's *Text-book upon Pathogenic Bacteria*, and Günther's *Bakteriologie*.

its morbid histology, but also with its parasitology. How essential this knowledge is may be appreciated when it is known that the morphologic pictures recognized as diseased conditions of organs and tissues, and the physiologic consequences recognized clinically as symptoms of disease, may all be primarily charged to the presence and activity of microscopic parasites. Tuberculosis, for example, is not only that disease in which conglomerations of tubercles, cheesy masses, and cavities appear in various organs, or that disease in which the microscope defines the elements of the individual tubercle; but it is all of this, plus something more—that is, the micro-organism of tuberculosis, which we now believe to be the cause of the disease.

Parasitism in its gross forms was long ago recognized, both in the animal and the vegetable kingdoms; and it was likewise known that certain parasites of animals and plants proved detrimental to their hosts, and that this harmful influence might even cause the death of the host. Long before the era of bacteriology it had been determined that certain animal organisms were parasitic in man, and several grave or even fatal human maladies, as those produced by the tapeworms, especially the echinococcus, and by the guinea-worm, were traced directly to their presence. Among the Arachnida the itch-mite has historic notoriety. And even microscopic parasites were not unknown before the beginning of bacteriologic science, as is shown in the case of the *Trichina spiralis*. That a world of organisms, microscopic in size and deadly in effect, lay hidden in the organs and tissues of numerous morbid affections in man was scarcely dreamed of until the perfection of the microscope, the improvement of technic, and the application of modern methods of biologic inquiry to the study of human diseases opened the way to the new knowledge relating to microscopic animal and vegetable parasites. With these microparasites and their disease-producing tendencies in the human flesh we shall now concern ourselves.

The inhabitants of this microbiologic world are occupied in many of Nature's phenomena, of which disease in animals and plants is but one. A large variety of the representatives of plant life, especially the great group known as bacteria, are important agents in fermentation, putrefaction, and decay, assimilation and growth of higher plants, etc., and some of the lowly animal micro-organisms are similarly engaged in extrinsic work, both constituting the *saprophytic* organisms, so called because of their peculiar property of obtaining nutrition from dead and decomposing organic matter. With that group of saprophytic micro-organisms which never invades the human body, and often described as *obligate saprophytes*, we here have little to do; but we cannot ignore entirely the great group of saprophytes, since some of its most important members carry on both an extrinsic and an intrinsic existence, so far as the human being is concerned; that is to say, they may be both saprophytes and parasites in the course of their life history, and hence they are called *facultative parasitic*, if preferably saprogenous though capable of becoming parasitic, or *facultative saprophytic*, if by nature parasitic while still capable of flourishing outside of the animal body. Then there is, as far as our present data enable us to judge, a class of micro-organisms which can subsist only in the living animal host, being, therefore, *obligate parasites*.

Parasitism is a product of evolution. This must never be lost sight of in studying any of its manifestations, since many variations will thus be

explained. Parasitism is a late biologic process in point of evolution, having been acquired after the free-living state of organic existence had been perfected. Its various adaptive stages can be seen even now, obligate parasitism representing the highest state of adaptation, with all intermediate variations to the state of obligate saprophytism. This evolution is going on about us day by day, and, recognizing its operation, we are not surprised to find that the list of parasitic organisms is gradually receiving accessions from the saprophytes. Nor is it surprising to find that, as the knowledge of the life history of many microparasites broadens, more importance is attached to the intermediate stages of their evolution.

As in general parasitology, so in the case of the human microparasites, the results of this foreign biologic occupation are various. Two factors must always be considered: the parasite, and the organism invaded by it, or the *host*. The parasite may choose as its abiding-place or *habitat* only the exterior or surface of the host's body, being then *ectoparasitic*; it may dwell solely in the interior of the host's body—in the alimentary tract, in the organs or tissues or circulating fluids—being then *entoparasitic*; or an ectoparasite may find its way into the interior, there to thrive with more or less success. The name parasite, as it is understood in ordinary parlance—a being living at the expense of another—defines the underlying cause of human microparasitology in most cases, the question for the parasite being one of nutrition and life dependent on another living being. The host may be variously affected by this foreign tenant. Often no harm follows, the presence of the parasite being wholly inconsequential. Again, the effect may be one of benefit to the host and of usefulness so great as to be indispensable; but this is not always so, and the parasitic invader exacts from the harboring organism various penalties. These harmful effects are shown by perversions of the normal conditions in the host—by morbid processes local or general, mild or severe—or in other words, by *disease*. So that the group of microparasites which especially concern us at this time is the great class of *disease-producing* or *pathogenic microparasites*. The extreme penalty, that of death, is, unfortunately for the longevity of the human race, only too frequently exacted by these depredatory micro-organisms. But the human organism does not remain passive when infested by harmful parasites, and in consequence the latter often suffer various degrees of restriction in their ravages, leading to a cessation of their activity (manifested in the host by arrest of disease) or to their expulsion or entire destruction (signalized by recovery from disease).

These considerations concerning parasitology apply in general to all parasites, macroscopic and microscopic, animal and vegetable. Our present purpose necessitates attention only to the microparasites; but even these, as has already been remarked, are represented by members both of animal and plant life. At this point, therefore, the first great subdivision of microparasites may be made into *vegetable microparasites* and *animal microparasites*. Of the animal microparasites, we shall consider only the unicellular forms, or protozoa.

Both from their numbers and their relative importance in pathology, the vegetable microparasites are entitled to priority of description. These microscopic disease-producing plants, often classed with the fungi on account of the absence of chlorophyl in most of their representatives, are conveniently divided into three great classes: the *fission-fungi* or *bacteria* (*schizomycetes*),

the *budding fungi* or *yeasts* (*blastomycetes*), and the *filamentous fungi* or *moulds* (*hyphomycetes*). We shall treat them in two parts: (1) The pathogenic bacteria; (2) Pathogenic budding and filamentous fungi.

THE PATHOGENIC BACTERIA.

General Morphologic Considerations.—The minute unicellular plants comprising the great group of bacteria, while apparently of simple structure, are nevertheless but little known so far as the finer morphologic details and their significance are concerned. Much of this lack of knowledge must be ascribed to the excessive minuteness of the bacterial cells, some of which are at the extreme range of microscopic vision as it is perfected to-day. On this account the *classification of bacteria* is still in an imperfect state, and, while much progress in systematic bacteriology has recently been made by the introduction of new methods (like flagella-staining), many of the morphologic features on which an accurate differentiation must be based are still undetermined. None of the schemes of classification thus far advanced is free from objection, but this is not a serious matter so far as the pathologist is concerned. For the present purpose, therefore, the subject of classification will be largely ignored, while retaining that nomenclature most widely accepted. It must be borne in mind, however, that both classification and terminology are far from secure at present.

The primary division of pathogenic microbes according to their shape into *micrococci* (*coccaceæ*, Migula), *bacilli* (*bacteriaceæ*, Migula), and *spirilla* (*spirillaceæ*, Migula) is generally satisfactory, and the subdivision of these families into genera, also on morphologic grounds, is likewise quite acceptable. The final differentiation into species and varieties depends chiefly on physiologic attributes, and here difficulties are encountered. This scheme of classification is useful in practice; its imperfections depend not only on an ignorance of morphologic details, but also on the wide range of variation, both morphologic and physiologic, to which bacteria are subject. This is illustrated by certain well-known pathogenic bacteria, as, for example, the so-called *bacilli* of diphtheria, of tuberculosis, and of glanders; for the tendency now is to remove these organisms from the bacilli family, and to place them among the family of thread fungi (*chlamydobacteriaceæ*, Migula), to which the important class of actinomyces belongs.

As to the general morphology of bacteria, we may say that the pathogenic bacteria are unicellular, chlorophyllless, microscopic plants, varying considerably in shape and size, and very susceptible to changes in environment by which morphologic variations of considerable range are produced. The *cellular substance* seems to be a vegetable protoplasm with certain metaplastic granules reacting like fat, starch, and sulphur. A *cell-wall* bounds this protoplasmic mass and bears a close resemblance to a hardened external layer of mycoprotein, although some species possess a cellular envelope giving the microchemical reactions of cellulose and allied carbohydrate substances. Regarded in the light of analogy with other simple microscopic organisms, it is highly probable that bacteria possess a nucleus, though it remains for future investigation fully to decide this point. Such double staining reactions as bring out the "metachromatic bodies," and those following the application of the Romanowsky stain in certain species, are highly suggestive in this direction. The *capsule* which invests some pathogenic bacteria is often an

artefact due to a swelling and distortion of the cell-wall. In those few species in which it is produced by vital activities, it apparently results from a softening or jelly-like metamorphosis of the outer portion of the cell-wall. Another striking structure, also related to the cell-wall and capsule, is the *flagellum*. These protoplasmic, whip-like appendages of the motile species are presumably part of the cell-wall, and are not in direct continuity with the internal protoplasmic mass.¹ A *sexual differentiation* has not been determined for bacteria, if indeed it exists; although the irregularities manifested by these organisms in shape and size, and the presence of various chromophilic substances within them, may ultimately be shown to have some significance in this direction. This may also be true of the process of flagellation in certain forms, particularly those in which the flagella are set free or assume unusual proportions (like the giant flagella of the malignant edema bacillus).

Multiplication and Reproduction.—According to our present knowledge, bacteria multiply by a process of simple division or *fission* in one or more planes depending on specific characteristics, and by a process of *sporulation*. The latter mode occurs when a resting or resisting stage is called for; the former is the usual method during the active vegetative stage. Of the *endosporous* mode of sporulation, our knowledge is quite precise; but there is considerable obscurity concerning the details of *arthrosporous* reproduction. Probably, as more is learned about sporulation, it will be found that the method of perpetuation by endospores is the common phenomenon among bacteria, judging from analogy with other microscopic fungi and from the prevalence of sporulation or seed-formation in plant forms generally.

Vital Activities.—From the standpoint of pathology, the most significant life phenomenon of pathogenic bacteria is that of *poison-production*, to which brief reference will now be made. That toxic substances are elaborated by bacteria, both within the living host and *in vitro* under experimental conditions, has been satisfactorily demonstrated. To what extent these poisons are generated from the albuminous substratum in which the bacteria grow, and to what extent from the internal metabolic activities of the bacteria themselves, are not determined. Probably both modes of elaboration are called upon in the case of bacteria. In the living body the part played by the living cells and juices is no small one in making up the picture of a given disease. The poisonous products of bacterial activity are the *ptomaines*, a class of crystallizable alkaloidal bodies, generally originating from the bacterial decomposition of dead animal matter; the *toxins*, poisonous substances contained in the bodies of living or dead bacteria or secreted by them; the *toxalbumins*, noncrystallizable and presumably proteid bodies not intimately associated with the protoplasm of the bacterial cell. The so-called *toxoids* are modified toxins in which the original potency has been lost spontaneously, as by age, or by such influences as heat, but which still are capable of conferring artificial immunity. It is to such toxic substances that the pathogenic micro-organisms owe their disease-producing power, contrary to the belief once current that they inflicted damage on account of their presence as foreign bodies in the organs

¹ But it must be remembered that, except in the case of certain large bacteria studied under exceptionally favorable conditions, no one has ever seen flagella in the living bacterium. Certainly nothing is known about their formation and fate from actual observation.

and juices of the host. The invasion of poison-producing bacteria and the sum total of the phenomena attending their presence in the body are known as *infection*. In the course of an infection, however, the animal organism does not remain passive, but through various agencies endeavors to inhibit the activities or to destroy the offending microparasite. Certain cells, both free and fixed, respond to the irritating influences of the parasite, and, by inhibiting or destroying the vitality of the micro-organism and by taking its body into their substance (*phagocytosis*), aid in ridding the body of the invader. Besides this mode of defence, the invaded organism possesses the power of annulling or neutralizing the toxicity of bacterial poisons by virtue of the elaboration of antidotal substances through the agency of its living cells. These protective bodies appear in the animal juices, notably the blood-serum, and several of them are now known. Thus the defensive proteids of natural immunity (inherent in the organism from birth), supposed to be excreted by the leukocytes and to reside normally in the blood-serum, are called *alexins*. Substances which appear during spontaneous or artificial infection or intoxication are known as *antibodies* (*Antikörper*) and *antitoxins*. Still another class of substances resulting from infection or intoxication, also appearing in the blood-serum, is capable of arresting the motility of motile species and of causing coherence or agglutination of the living or dead bacteria; these are the *agglutinins*, and they are closely allied to the *bacteriolysins*, which cause disintegration and solution of the bacteria. The exact nature of these interesting substances, which are all considered as proteids, has not been fully determined; but the most popular assumption is that they are unorganized ferments or enzymes, and on this basis Ehrlich and Morgenroth have recently elaborated an hypothesis to explain their function in immunity.

THE PRINCIPAL PATHOGENIC BACTERIA.

The Bacillus of Anthrax.—It was the discovery of the anthrax bacillus as the essential cause of anthrax that constituted the first satisfactory demonstration in pathologic bacteriology.

The specific micro-organism of this affection is a comparatively coarse bacillus dividing by fission in the vegetative state, leaving partition-lines that are usually plainly visible, and tending to form long chains when dividing in unhampered surroundings. A resisting stage with formation of median endospores is also a part of the life history of this bacillus, although it never forms spores in the body of the living host. The range of morphologic variation is not wide, the chief being in the length of the rod and in its thickness. In the animal organs and juices it tends to become a shorter rod than in artificial media, and an envelope, apparently a true capsule, appears about it in stained preparations, especially of anthrax blood. The physiologic characteristics of the anthrax bacillus are also unusually constant, both in natural and artificial environment. Except for a slight deviation in proteolysis and rate of growth, artificial anthrax cultures show little change even after prolonged stay in the laboratory, and the pathogenic activity of the bacillus is retained with unusual persistence under artificial conditions. On this account and because of the readiness and certainty of its effects in susceptible animals, it is the favorite bacterium for laboratory experimental demonstrations.

In all probability this bacillus had its natural habitat in surface soil or upon surface vegetation like grass, and passed here the saprophytic stage of its evolution. From this normal



FIG. 75.—Colony of bacillus of anthrax, slightly magnified (Flügge).

abode it found its way as a parasite first into grazing animals, hence the wide natural prevalence of anthrax among wild and domesticated ruminants. Infection in man does not seem to be possible except through an intermediate animal host, and most commonly the disease follows the handling of infected living or dead sheep and cattle, their hides, and the bristles and hair of animals dead of the disease. Possibly suctorial insects may also carry the infection from these animals to man, but direct contact with the affected animal or a product derived from it can usually be demonstrated as the mode of invasion. Woolsorters' disease is anthrax commencing in the respiratory organs, and is due to inhalation of infective dust or wool-fibers. Swallowing the material may produce intestinal anthrax, and there is reason to believe that eating underdone meat of infected cattle or sheep may incite the same infection.

Morbid Action.—Anthrax in man is a disease not clinically uniform.

This irregularity depends principally on the avenue of invasion, of which there are three chief ones—the skin, the respiratory mucous membrane, and the intestines.

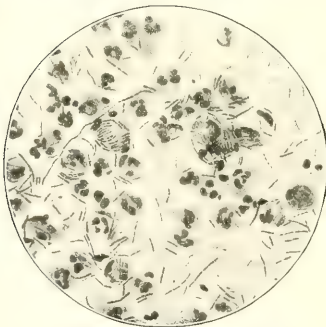


FIG. 76.—Anthrax bacilli in exudate, showing phagocytosis. $\times 300$ (Karg and Schmorl).

The characteristic anatomic lesion of cutaneous anthrax is the malignant pustule—a circumscribed, discolored swelling of the surface, varying in size within moderate limits and resembling somewhat an ordinary furuncle. Its color is usually a deep reddish, and the surface may be smooth or broken and covered with dried secretion, or it may be blackened and necrotic in older lesions, resembling a miniature volcanic crater, from which issues a

purulent or seropurulent and often bloodstained discharge. It is often surrounded by vesicles like a string of pearls. In its early stages the pustule is indurated, then it becomes succulent, and finally filled with fluid or semifluid purulent material. This cutaneous focus owes its origin to the positive chemotactic influence of the bacillus and its products, resulting in the accumulation of a serosanguinolent and cellular exudate in the papillæ and the corium, the latter layer becoming packed with multinuclear leukocytes. In the superficial

portions and the papillary body the anthrax bacilli are encountered, usually in large numbers, dispersed both in the blood-vessels and in the spaces of the tissues or between the cells of the exudate. In chronic malignant pustule the bacilli may be entirely wanting. The densely accumulated leukocytes seem to make a barrier against the deeper progress of the micro-organisms. In different individuals there seems to be a marked variation in the number of bacilli in the pustules, in their diffusion, and especially in the phenomenon of phagocytosis. The latter process is very active in some cases, most of the polynuclear leukocytes and large mononuclear hyaline cells in a smear-preparation of the discharge containing bacilli in various stages of disintegration. Even where phagocytosis is not so pronounced, there seems to be a harmful influence at work upon many of the bacilli, which fail to stain in the usual manner. Both in malignant pustule and in general anthrax infection the principal changes are a serous, serofibrinous, or seropurulent inflammation with more or less hemorrhage and necrosis. There is frequently a cloudy swelling of the viscera, and the spleen is so swollen as to give the synonym "splenic fever" to anthrax, although this is not invariably present in man. But fatal general anthrax may occur in man, with lesions so insignificant as not to attract attention, producing a veritable anthrax septicemia. Hemorrhages are frequently observed in the alimentary mucosa in intestinal anthrax, and have also been noted in the mesenteric and bronchial lymph-glands, the pancreas, and the brain. Necrosis and ulceration may appear in the hemorrhagic areas. A metastatic embolic infection of the gastric and intestinal mucosa, with resulting hemorrhagic necrosis and submucous edema, has been occasionally seen in cutaneous malignant pustule. Other anatomic lesions inconstantly noted in anthrax are tonsillitis, bronchitis, pneumonia, pleuritis, adenitis, endocarditis, and peritonitis.

So filled are the capillaries of infected viscera, like the liver, with anthrax bacilli, that the theory of mechanic plugging was for some time held to explain the pathogenic action of these bacteria. The filling of the capillaries in the important viscera and a decomposition of the blood were considered as the principal factors. This theory is no longer held, its inadequacy being shown, for instance, by the cases of fatal anthrax with few or no bacilli in the blood-vessels of important organs. Gradually it was learned that poisonous products were elaborated by the growth of anthrax bacilli under artificial environment, and some of these products were fatal when used on susceptible animals, although not followed by typical symptoms. Some confusion as to the exact identity of this anthrax toxin still exists, but most authorities maintain that it is only on the basis of a toxic action that the phenomena of spontaneous or experimental anthrax can be explained. Whether the blood-vascular or lymph-vascular channels are chosen for the spread of the organisms from the primary focus is not positively determined, though the latter route seems the more probable one; and the enormous increase of bacilli so often seen in the blood-vessels is to be regarded as a late or agonal phenomenon in the disease, the progress of which to this point results from the toxemia. Evidence in favor of this presumption is afforded by the equally slow progress of intravenous and subcutaneous experimental anthrax and by the more rapid course of the disease when beginning in regions well supplied with lymphatics, like the face, neck, and mucous membranes.

Historically it is of interest to note that anthrax is one of the infectious diseases in which bacterial therapy was first attempted. Pasteur and his followers tried to produce an active immunity in sheep by vaccination with an anthrax virus attenuated by heating virulent cultures. As now perfected, this protective vaccination in sheep and cattle has a practical commercial value, although the results are not always certain and the period of immunity is often quite short. Anthrax is also one of the infections in which experiments in serum immunity were first tried, but thus far the results in this direction have not been encouraging from the therapeutic standpoint.

The Bacillus of Typhoid Fever.—No one who works with the two groups of bacilli, the colon and the typhoid, and especially with the intermediate forms, can fail to be impressed with the narrow margin of physiologic differentiation separating them. Many are now inclined to consider the typhoid bacillus as a modified colon bacillus, as a fecal bacillus unaltered morphologically, but with a few acquired physiologic characters probably due to its more or less prolonged sojourn under saprophytic conditions. This view, proclaimed by Rodet and Roux about ten years ago, has

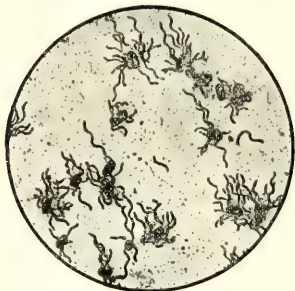


FIG. 77.—Bacillus of typhoid fever, from an agar-agar culture six hours old, showing the flagella stained by Löffler's method. $\times 1000$ (Frankel and Pfeiffer).

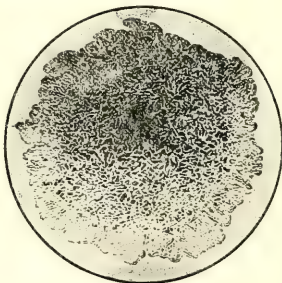


FIG. 78.—Bacillus of typhoid fever: superficial colony two days old, as seen upon the surface of a gelatin plate. $\times 20$ (Heim).

been steadily gaining ground, although it is by no means firmly established. It seems, however, to explain most readily the otherwise anomalous behavior of typhoid fever under natural conditions, both with reference to its clinical and pathologic features.

At present we are inclined to regard the morphology of the typhoid group as more constant than that of the colon bacillus, although this may only be a matter of limited observation. Both are nonsporogenous, the clear spaces in the bacterial cell, once supposed to be spores, resulting from plasmolysis. The physiologic differential features of the extreme types, as we study them under the artificial conditions of the laboratory, seem sufficiently marked to be distinctive. It is only when the intermediate or linking types are studied that skepticism is aroused as to the fixed nature of such characteristics as the fermentation reaction, milk coagulation, indol production, and the like; and even the agglutination phenomenon can scarcely be said to have an absolutely fixed value.¹

¹ One of the most significant arguments for the close relationship of these bacterial groups seems to be afforded by the now generally adopted practice of "rejuvenating" bacilli

Although the typical specific bacilli have only occasionally been demonstrated in drinking-water, the latter is nevertheless held to be the usual medium of contagion, becoming contaminated from the feces or urine of previous cases of typhoid. It appears that the organism may occasionally be carried by other foodstuff, like milk or oysters; and by certain plants, as radishes or celery, contaminated with infectious material like sewage, or washed with contaminated water. The longevity of the typhoid bacillus even in distilled water is considerable, and it probably leads a prolonged existence under more favorable nutritive saprophytic conditions. Another mode of contagion, the importance of which is being more and more recognized, is by means of certain insects, particularly flies, which feed upon human dejecta and then light upon various articles of food; upon this hypothesis certain extensive outbreaks of typhoid fever in military camps have been explained. Here the fly does not act as an intermediate host, but only as a mechanic carrier of the parasites. The possibility of air-borne typhoid must be admitted, although it has not been proved. In most cases the feces and



FIG. 79.—Typhoid bacilli, showing the Widal agglutination reaction (Slater and Spitta).

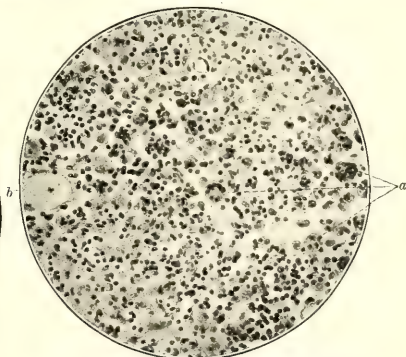


FIG. 80.—Medullary swelling in a typhoidal lymph-gland in a state of large-celled hyperplasia, showing at (a) large multinuclear cells (macrophages), $\times 235$ (Karg and Schmorl).

urine of typhoid patients appear to furnish the infecting germs, their presence in large numbers in both having been positively determined.

Morbid Effects.—That bacilli of the typhoid group are the essential etiologic factors in human typhoid fever seems satisfactorily demonstrated, even though experimental proof, such as may be obtained in some other microbial affections, has not been secured. Typical typhoid fever presents a clinical and anatomic picture of remarkable uniformity, and in all well-developed cases the typhoid organism may be found in the spleen and mesenteric lymph-glands. The fundamental gross lesions are swelling and, later, of the colon group secured from saprophytic surroundings, as from water; by growing them for several generations under the artificial laboratory environment before making physiologic differential tests. In the early generations on plate cultures, much divergence is manifested by the progeny of the individual organisms; and to overcome this and reduce them to the "normal" typical condition, they must be rejuvenated. It may well be doubted whether the characteristics remaining from the saprophytic sojourn, or those acquired under laboratory environment, are really the normal. Many of the acquired characteristics make a suspiciously typhoid-like behavior in a so-called colon bacillus.

ulceration of the solitary and agminated lymphoid follicles of the intestinal mucosa (ileum, or ileum and colon), the tumefaction of the mesenteric nodes and of the spleen. More intense infection is shown by cloudy swelling of the viscera and by further changes, like cholecystitis, cystitis, pneumonia, laryngitis, osteitis, meningitis, etc. Thrombosis, especially of the larger veins, is rather common as a complication. The point of excitation in typical cases seems to be the lymphoid follicles of the ileo-cecal region, and in mild cases the intestinal lesions are confined to this locality. A diffuse swelling of the solitary glands and Peyer's patches appears, extending up the small bowel and sometimes into the colon, and the mesenteric glands also swell, those in the line of absorption from the ileocecal region first. From the more recent and precise histologic studies, especially those by Mallory, it appears that the tumefaction of the intestinal, mesenteric, and splenic lymph-apparatus is due to the excessive proliferation of phagocytic endothelioid cells arising from the lymph-spaces, lymph-vessels, and endothelial layers of the blood-vessels. These cells are diffusely scattered throughout the swollen follicles and glands in immense numbers, or accumulated in large groups; and they manifest pronounced phagocytic activity, as well as multiplication, or retrogressive changes. In the finer blood-vessels they may occlude the lumen, such occlusion being often accompanied by a deposition of fibrin. In some cases the appearance of similar intravascular plugs in remote organs is probably of an embolic nature, although an endothelial proliferation may apparently be excited in the tissue-spaces and blood-vessels of parts remote from the abdomen.

Peculiar collections of cells in the liver, formerly known as lymphoid nodules, are quite constant in typhoidal affections; these are now known to be focal areas of coagulation-necrosis. They may also appear in the kidneys and in the spleen, and in some cases at least they are related to a minute blood-vessel occluded by an endothelioid cell-mass or a fibrinous, or cellular and fibrinous, thrombus. In other foci no connection with occluded vessels can be seen, the accumulations seemingly being induced by the local out-pouring of some toxic fluid from the vessels.

The typhoid bacillus at times exhibits pyrogenic properties; and abscesses of the mesenteric glands, spleen, liver, and bones, as well as suppurative cholecystitis, pleuritis, and meningitis, may be caused by it. The pulmonary affection of typhoid fever usually takes the form of bronchopneumonia, in which aspiration-infection plays a role, the lesion containing either foreign bacteria alone or such bacteria and the typhoid bacillus. Lobar or croupous pneumonia also occurs—the result, as a rule, of infection with the pneumococcus. Typhoidal meningitis may take the form of a hemorrhagic pachymeningitis, of serous or suppurative leptomeningitis. In the latter case the exudate consists both of ordinary pus-cells and endothelioid elements, and may be accompanied with an obliterative endarteritis due to subintimal accumulations of small round cells.

Atypical typhoid fever with no trace of intestinal ulceration and little or no lymphoid swelling of the intestinal mucosa, taking the form of a septicemia, has been repeatedly noted. But it is more common for the bacilli to confine themselves to the intestinal lesions, mesenteric glands, spleen, bone-marrow, and gall-bladder, instead of invading the general blood-stream; so that the extensive histologic alterations above noted must, in part at least,

be ascribed to some product of bacterial, or bacterial and cellular, activity. As to the nature of this toxic substance, but little is known; in any case, the poison is not powerful, and the results of experimental efforts to induce typhoid fever by the use of living or dead bacilli, or substances extracted from them, have been rather indefinite.

Immunity and Bacterial Therapy.—Positive knowledge concerning the source and nature of the typhoidal poison is still unattained, the general view being that the substance is contained in the bodies of the bacilli, although other evidence suggests that, in the animal body at least, a diffusible toxic agent is liberated. Experiments in artificial immunity are not satisfactory, for the reason that laboratory animals are for the most part susceptible only to intraperitoneal injections, which produce merely a peritonitis. Subcutaneous abscesses have been obtained experimentally, and purulent meningitis by subdural inoculation; and death sometimes follows large subcutaneous injections. But animals may be immunized by gradually increasing doses of living or dead typhoid bacilli, the peritoneal cavity becoming more and more resistant to infection, and the serum of such animals develops a specific bactericidal (bacteriolytic or disintegrating) property against the typhoid bacillus, becoming a weak antitoxin with both protective and curative action. Practically typhoid antitoxic serum has been a failure; but protective vaccination with attenuated typhoid cultures, which has been extensively carried on in the British army in Africa, is more promising. The composition of the bactericidal and antitoxic agent in the serum of animals made immune by artificial means or by reason of an attack of typhoid fever is undetermined, and the same must be said of the so-called agglutinins, which give to the serum its capacity of causing agglutination of typhoid bacilli. This does not, of course, detract from the wide and successful application of the agglutinating or clumping reaction in clinical diagnosis.

The Colon Bacillus.—Soon after birth the intestines of man—and most, if not all, other mammals—are occupied by this parasite, which has been found in the intestinal contents of most vertebrates. Both its widespread occurrence and its existence in healthy animals suggest that the colon bacillus occupies an important part in the animal economy. It seems, however, that the early development of newborn guinea-pigs is not impeded by keeping these organisms out of the bowels; but how far this is applicable in more prolonged existence, or in man, experimental facts do not show. In a state of health in adults, there can be no question of the usefulness of the intestinal flora in which *Bacillus coli communis* predominates, as it doubtless aids in digestive operations and contributes to the formation of gas so necessary to the maintenance of abdominal and thoracic equilibrium. Being so constant, if not indispensable, an inhabitant of the intestines of vertebrates, and being evacuated with their feces, it is not surprising that the members of this group are found widely distributed in nature; and when one considers all the various vicissitudes to which animal feces are subject, entailing great changes in the environment of the contained bacteria, the

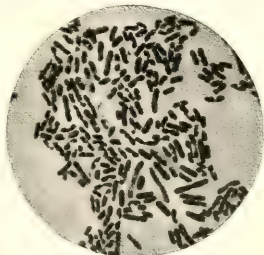


FIG. 81.—*Bacillus coli* (vacuoles). $\times 1000$ (Migula).

numerous subvarieties of the colon group seem, in part at least, explicable. That members of the colon group of bacteria are subject to wide physiologic variation is well known—there being, indeed, a chain of varieties reaching from the colon to the typhoid group, as already indicated. The extreme so-called “typical” colon bacillus causes fermentation and proteolysis, produces indol, and coagulates milk; but these functions show gradual modifications among the intermediate varieties. Morphologic variation is not striking among the colon bacilli cultivated in the laboratory, but extreme deviation from the ordinary rod has been noted of late in careful examination of organs, like the liver, harboring old latent bacilli of the colon group or recently infected. Here the micro-organism may appear as long threads, or shorter, broken streptococoid threads, or micrococoid (diplococoid) forms, some of extreme minuteness. A failure to recognize atypical forms has undoubtedly led to occasional faulty diagnosis of the bacterial species, since the irregularities may persist for several generations on artificial culture media.

Under conditions almost wholly unknown to us at present, this harmless or even useful bacterial messmate may become a harmful, deadly enemy, at times apparently beginning its pathogenic activity in the intestinal canal, which constitutes its home. Infantile diarrhea, diarrheal affections in adults, and certain dysenteries may be all due to bacilli of the colon group, at times quite typical, at others more or less atypical. In some of these cases there is little anatomic change, the process being incited by irritating foodstuffs or by perverted and toxic digestive products, which induce a lowered resistance, thus opening a way for the ravages of the bacteria. Under other circumstances, as in the case of appendicitis, strangulated hernia, intussusception, etc., mechanic lesions of various kinds may precede the destructive activity of the colon bacilli. Invasion of the gall-bladder and bile-ducts often follows injury from biliary calculi, although it is not positively determined whether the bacilli gain access from the bowel or by the blood. Exogenous infection by these organisms is also possible, as seen occasionally in wound infections. Foods contaminated by colon bacilli from outside sources have been at times found responsible for outbreaks of extensive food-poisoning, taking the type both of an intoxication (botulismus) and of an infection.

Morbid Effects.—An inflammatory reaction, sometimes suppurative, usually attends the advent of pathogenic colon bacilli in the human body. Almost any organ or any serous surface may be incited to inflammation, generally of an acute nature, and which is often followed by the production of serofibrinous or fibrinopurulent exudates. At times the colon bacillus alone plays the role of a pyogenic organism, although in the most severe manifestations of its activity, as in appendicitis and peritonitis, it is often mixed with the pyogenic cocci. It is responsible for many inflammations of the genito-urinary tract, particularly pyelitis, rarely also urethritis. Focal coagulation necrosis may be produced in spontaneous or artificial infections with this organism. Occasionally, in chronic and prolonged irritation with bacilli of the colon group—occurring, for instance, in neglected or unrecognized appendicitis—a large amount of new fibrous connective tissue with hyaline degeneration will form, and give rise to the production of more or less localized tumor-like masses occasionally mistaken for true tumors. Abscesses and fistulas may form in such masses. Whether a somewhat similar process, resulting in the production of fibrous tissue in the parenchyma of organs, as in the

liver and kidney (cirrhosis), may be induced by the colon bacillus or its allies (so-called paracolon bacilli), is still unsettled, although certain investigations point strongly to this conclusion. An acute and rapidly fatal process taking the form of a septicemia also at times occurs in the course of an acute or subacute colon-bacillus infection.

Immunity and Bacterial Therapy.—The poisonous substance produced by the colon bacillus, to which its various pathogenic effects are due, is, like that of the typhoid bacillus, not definitely determined; but, as in the case of the latter, it is supposed to reside, for the most part at least, in intimate combination with the protoplasm of the bacterial cell. Experimental infections with the various colon bacilli bear a close resemblance to those produced by the bacillus of typhoid fever, essentially the same phenomena as to immunity, agglutination, and the production of a protective or curative serum being witnessed. No therapeutic results of practical value have as yet been obtained, except perhaps in acute tropical dysentery.

Pathogenic Bacilli Resembling the Colon-Typhoid Types.—

Besides the more typical members of the typhoid and colon groups of bacilli, a large number of nonpathogenic and pathogenic bacilli have been described, which show but a shade of deviation, chiefly in physiologic differential tests, from one or another of the types. Some of these organisms, which many observers believe are but varieties of the colon or typhoid species, are associated with important pathologic processes, and several of them are doubtless destined to assume great importance in pathology. Thus there is a group sometimes separately considered as *Bacillus enteritidis*, to which several sub-species belong, the features of which are strongly suggestive of relationship with the colon bacillus, and which are concerned in various diarrheal disorders and intoxications caused by their presence in meat. Also allied to this group are the *hog-cholera bacillus*, now generally accepted as the exciting cause of this disease in swine, and, more important still, the so-called *Bacillus icteroides*, claimed to be the micro-organism of yellow fever. Both these organisms present biologic evidence of affinity with the human colon bacillus; moreover, they resemble each other so closely that certain investigators have considered them identical. Both are pathogenic under experimental conditions, producing necrosis and showing other evidence of similarity as to their toxic products, immunizing substances, and agglutinins. In the dog, the *Bacillus icteroides* causes symptoms and lesions suggestive of those in yellow fever, and strong claims are made for the specificity of this micro-organism. No matter what view may be taken about the relationship of the hog-cholera and yellow-fever bacilli, it must be remembered that both these micro-organisms are closely allied to the larger colon-typhoid group, and that climatic and environmental conditions and peculiarities in the host may account for the slight variations which the bacteria show and for the wider variation exhibited by the diseases which they are supposed to induce. Such consideration also applies to other typhoid-colon forms, as *B. dysenteriae* and *B. paradoxus*, obtained from cases of acute tropical dysentery, and by some believed to stand in a causal relationship, and to the *paracolon bacillus*, *pseudotyphoid bacillus*, *bacillus of mouse typhoid*, and a number of other organisms, variously designated by different investigators.

Bacillus Mucosus Capsulatus (*the Pneumobacillus of Friedländer and its Related Forms*).—As the type of a large group of bacilli, which agree in general cultural behavior and in the possession of a capsule (espe-

cially when obtained from animal secretions), we may consider the pneumobacillus of Friedländer. To this group, which comprises a large number of asporogenic, nonmotile bacilli described under different names by various observers, the designation *Bacillus mucosus capsulatus* has been given by several recent writers, who have systematically studied the various members.¹ The various individual representatives of the group, which are regarded as varieties or subvarieties, have been further divided into two chief classes, those more closely related to the pneumobacillus and those resembling the ozena bacillus, which stand as the extremes of the series. Polymorphism is characteristic of these bacilli, so that no system of morphologic classification is reliable. True capsular envelopes are formed by all the legitimate members of the group, sometimes when grown on an artificial medium, like blood-serum, sometimes only in the blood or juices of infected animals, sometimes under both conditions. So constant is this morphologic feature that from it the name *B. mucosus capsulatus* has been derived. In a general way, the physiologic characters are those ascribed to the typical Friedländer bacillus ;



FIG. 82.—*Bacillus mucosus capsulatus* from the sputum of a pneumonia patient. $\times 1000$ (Fränkel and Pfeiffer).

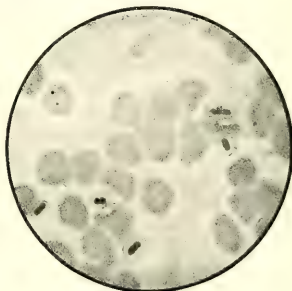


FIG. 83.—*Bacillus mucosus capsulatus* in blood. $\times 1000$ (Fränkel and Pfeiffer).

that is, a slimy, mucoid, profuse growth on agar and blood-serum ; a somewhat similar yellowish growth on potato ; a nonliquefying growth along the line of the gelatin stab, with a rounded, glistening, subspherical (“nail-shaped”) elevation at the surface ; variable fermentative function ; no indol production or proteolysis ; and decolorization by Gram’s method of staining. The cultural variations for the whole group are comparatively slight ; but the capacity of fermenting the sugars is subject to much variation, some members of the group never producing gas, and others causing abundant gas formation in media with various sugars. Staining after Gram’s method occurs at times. Many of the cultures have an aromatic odor, some are odorless, others fetid. The pathogenicity of this group, as tested by subcutaneous, intraperitoneal, or intrapleural injections in mice (particularly white mice), guinea-pigs, and rabbits, is also an inconstant feature. Almost all of the members prove pathogenic for mice in subcutaneous inoculations, although

¹ In this group are included, among others, the *Rhinoscleroma bacillus*, *Proteus hominis capsulatus*, *Bacillus capsulatus* of Pfeiffer, of Mandry, of Kockel, of Loeb, of Cohn, of Mallory and Wright, of Chiari, etc., *Bacillus mucosus capsulatus* of Fasching, of Paulsen, of Abel, etc., and still others, twenty-two in all, enumerated by Fricke in his analysis of the group. *Bacillus lactis aerogenes* is also closely allied with the group of capsulated bacilli.

some, like the typical pneumobacillus, only prove fatal when inoculated into the peritoneal cavity or the lungs. A few do not kill mice. Guinea-pigs prove refractory to several capsulated bacilli, and rabbits to others. Sometimes one and sometimes another of these species of rodents will succumb to the infection, while in a few instances all three species react.

Evidently the pneumobacillus and its allies belong to a group of facultative saprophytes, since they have been found in dust, mud, air, and canal-water. At times they appear in the nose, mouth, trachea, and intestines of healthy human beings.

Morbid Conditions with which Bacillus Mucosus Capsulatus is Associated.—These organisms have been found in a variety of pathologic conditions, at times alone, and again in company with other pathogenic bacteria. In some instances they appear to be the sole exciting factor of the morbid process.

The first disease in which the capsulated bacilli were found, and which led to the designation pneumobacillus,¹ was *pneumonia*, from which the organisms were isolated and studied by Friedländer in 1883. We now know that in 5 to 10 per cent. of cases of croupous pneumonia in man, and in a somewhat higher percentage of cases of bronchopneumonia, these capsulated bacilli are found, usually mixed with other micro-organisms. That it can cause typical acute lobar pneumonia is doubtful; but there is no question as to its etiologic role in other forms of pneumonia, especially bronchopneumonia.

As complications of the pulmonary affection, such lesions as *pleuritis*, *pericarditis*, *endocarditis*, *bronchitis*, *otitis*, and *meningitis* have been observed, with capsulated bacilli in pure or mixed cultures. Infection of the genito-urinary tract with the production of pyelonephritis has been ascribed to members of this group; and they have further been found in puerperal metritis, pulmonary and hepatic abscess, gastro-enteritis, and in various catarrhal conditions of the upper air-passages, including the accessory nasal sinuses. In all these situations an acute or chronic inflammatory reaction, usually with suppuration, is induced. Still more important is the association of capsulated bacilli with *hemorrhagic septicemia*, and several well-authenticated cases of this disease in the newborn and in adults are now recorded, in which bacilli with practically identical morphologic and physiologic features were obtained in pure culture. Aside from the cutaneous, submucous, and subserous hemorrhages found in this malady, which seems to be a distinctive affection with some clinical affinity with typhus fever, there are marked changes in the blood-vessels, with fatty degeneration of the endothelial lining, leading to rupture and hemorrhage. A profound destructive effect is also produced on the red blood-cells, the pigment of which accumulates in the liver, spleen, and kidneys. Emboli of liver-cells have been noted. In atrophic rhinitis, especially the form accompanied by fetid purulent secretions (*ozena*), one of the bacilli of the group is so often found as strongly to suggest an etiologic significance. Likewise in rhinoscleroma,

¹ In his original communications Friedländer called this organism a micrococcus (pneumococcus), and from some of his descriptions it looks as though he must at times have had *Micrococcus lanceolatus* under observation, especially in smears of pneumonic sputum, exudate from the lungs, and in the blood of animals. But the cultures on nutrient jelly all seem to have been those of capsulated bacilli with the nail-shaped character. It is now conceded that Friedländer erred in attaching too wide an etiologic significance to his "pneumococcus."

a chronic granulomatous affection beginning in the nose and often extending to the adjacent mucous or cutaneous surfaces, capsulated bacilli are found, especially as inclusions in large vacuolated cells of the granulomatous tissue and in the secretions, and these bacilli are now placed in this group.

Practically nothing is known concerning natural and artificial immunity against pneumobacilli, and efforts to establish specific agglutination tests for differentiating the various forms have thus far given inconstant results.

Proteus Vulgaris and Related Bacilli.—There is a group of bacteria apparently composed of a number of varieties, as the prototype of which *Proteus vulgaris*, or *Bacillus proteus* of Hauser, may be selected.¹ As originally described by Hauser in his work on putrefactive bacteria, the proteus bacilli are pre-eminently saprophytic, being the common organisms of putrefaction in dead animal and vegetable substances. The widespread occurrence of these organisms is evident from their relation to the putrefactive processes, and their presence in such media as air, soil, dust, water, and in various putrefying foodstuffs, is readily understood. Bacteriologists were for some time inclined to consider these bacilli as obligate saprophytes, and their occasional appearance in the human organism as a purely accidental occurrence. That this is in part true is evident from the fact that the bacteria of this group are found in such places as the mouth, stomach, and intestinal contents of healthy human beings. But there is overwhelming evidence that the harmless saprophytic proteus, under certain conditions, may assume a definite pathogenic role, either aiding in their harmful action other disease-producing micro-organisms, like the bacillus of diphtheria, the pyogenic cocci, the bacilli of tetanus and malignant edema, or pursuing an independent course as the excitant of morbid processes.

Variations in morphology are frequent among these bacilli; micrococcus-like forms, ordinary bacilli, and long filaments often appear in the cultures of a single race. Active motility and a profusion of flagella arranged radially about the bacterial cell are characteristic of most varieties of the group. The members most closely allied to the *Proteus vulgaris* type liquefy gelatin, and in gelatin plates a "swarming" or ameboid-like formation of offshoots occurs during the early liquefaction of a colony. Putrefactive odors are evolved during the peptonization of gelatin and blood-serum. Milk is coagulated and the casein digested. Indol and phenol are formed, and the sugars, with the exception of lactose, are fermented. Spores are not formed, and the growth is facultative anaërobic. These characters are subject to some variation, since certain members of the group have no peptonizing power, while of those having this function some liquefy rapidly and others tardily. The reaction to Gram's stain is inconstant. Moreover, it is claimed by some observers that particular methods of artificial cultivation are successful in changing several of the physiologic characteristics of a given race. In their pathogenic effects on laboratory animals, various proteus bacilli differ markedly. Some are seemingly harmless even when employed in large doses; others induce a chronic intoxication after injection. Following a subcutaneous injection, gradually spreading induration with cheesy metamorphosis may be induced, the animal dying finally in a condi-

¹ Other bacilli closely allied with *Proteus vulgaris* ("*Bacterium termo*" of the older microscopists) are the *B. albus cadaveris*, *Urobacillus liquefaciens*, *B. fatidus ozæne*, *B. proteus septicus*, *B. proteus lethalis*, *B. murisepticus pleomorphus*, *B. proteus fluorescens*, *B. dysenteriae liquefaciens*. *Proteus mirabilis* and *P. Zenkeri* are very similar to the typical *P. vulgaris*, if not identical with it.

tion of cachexia. But many cultures are actively pathogenic, producing prompt fatal results either by subcutaneous, intraperitoneal, or intravenous injections.

Pathogenic Effects in Human Beings.—The proteus group belongs to that rather small class of bacteria which excite disease indirectly through the contamination of material ingested as food. This effect is, of course, what would be anticipated from the constant association of these organisms with putrefaction and decomposition. An epidemic of meat-poisoning accompanied by hemorrhagic enteritis has been traced to proteus bacilli; and we have the record of an extensive outbreak of food-poisoning, characterized with vomiting, fever, and diarrhea, in which oatmeal containing proteus and colon bacilli seemed to be the cause.

Numerous instances of more direct pathogenic action of the proteus bacilli have accumulated in recent years; in many cases the proteus was associated with other pathogenic bacteria, as has already been mentioned. Thus in infected wounds, particularly those of a gangrenous or putrefactive tendency, proteus has been found with other micro-organisms; this is also the case in such conditions as ulcerative endometritis, in osteomyelitic pus, in ozena, and it is questionable whether the proteus here plays only a saprophytic role or is in part responsible for the pathologic process. In such affections as puerperal parametritis, meningitis, and brain-abscess (following middle-ear disease), gangrenous and purulent peritonitis, pulmonary gangrene and gangrenous pleuritis, proteus, while mixed with other micro-organisms, seems to take more than a passive part. Finally there are a number of conditions in which proteus alone was found; from the experimental evidence, it is highly probable that it may have been the sole pathogenic agent. In the last category comes a case of general peritonitis, one of appendicitis complicating an inguinal hernia, pleurisy, several instances of cystitis and pyelonephritis, ovarian abscess, mammary abscess, and liver-abscess. Proteus, in company with the colon bacillus, has been found in cholera infantum and in epidemic dysentery.

More serious still are the general proteus infections, in a number of which now recorded these bacilli appear to be the specific factors. Weil's disease (acute febrile icterus), epidemics of which sometimes occur, is ascribed to the action of a fluorescent member of the proteus group, which has been found unmixed in the urine, blood, and organs of fatal cases, the early observations of Jäger having been confirmed by several subsequent investigators. Probably some cases of infectious icterus and icterus gravis of the newborn, in which proteus was found, belong in the same class as Weil's disease. Proteus has also been described as the causative factor in several examples of hemorrhagic septicemia, where the original infection probably resulted from eating spoiled meat. In at least one instance the disease was epidemic, taking the form of hemorrhagic enteritis with fatal septicemia, thrombosis, hemorrhagic foci in the serous membranes and viscera; here an extremely virulent proteus race was obtained. The recent studies on the kedani disease of Japan are extremely interesting as examples of proteus infection through the wounds inflicted by an insect, a specific mite (kedani) closely allied to the harvest-mite (*Leptus autumnalis*). This epidemic disease, causing a mortality of about 40 per cent., appears in certain river-bottoms (after flood-water has subsided and decaying vegetation remains behind), infecting the individuals who harvest the hay and other fodder and are

bitten by the mites. After a brief incubation period characterized by local reaction at the site of puncture, the lymph-glands adjacent to the region bitten by the insects become swollen and painful, and further swelling affects the remote lymph-nodes. There is fever, running a typhoid-like course, and an urticarial exanthem. Nervous symptoms, bronchitis, and splenic tumor develop, usually with constipation; albuminuria follows, and death results in from ten to thirteen days. From the blood and organs of fatal cases a virulent bacillus with morphologic and cultural affinities with proteus has been repeatedly isolated. Toxic substances have been obtained in dead or filtered proteus cultures, and experimental immunity has been conferred on guinea-pigs either by the use of living bacilli in small doses, by dead bacilli, or by filtered cultures. The blood-serum of these animals possesses protective properties; it also agglutinates the proteus bacilli.

Bacillus Pyocyaneus.—There are bacilli constituting a class or group, of which the pathogenic *B. pyocyaneus* of Gessard makes one extreme, and the nonpathogenic, saprophytic *B. fluorescens liquefaciens* the other. Just how closely these races are united is hard to decide, although the finding

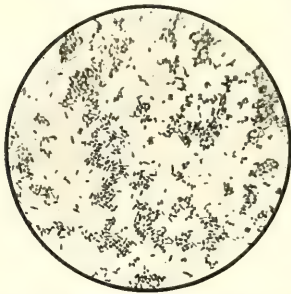


FIG. 84.—*Bacillus pyocyaneus*, from an agar-agar culture. $\times 1000$ (Itzerott and Niemann).

of various intermediate varieties tempts one to consider the pyocyaneus bacillus as a liquefying fluorescent bacillus, somewhat modified by adaptation to a parasitic existence. It certainly is suggestive to find that a culture of the fluorescent bacillus obtained from saprophytic environment may assume pathogenic properties after laboratory cultivation, and also to know that pyocyaneus bacilli have been encountered as transient parasites in the saliva, sputum, sweat, and gastric contents from human beings, here apparently leading a semisaprophytic existence, with no pathogenic proclivities.

In morphology, the members of the pyocyaneus group thus far identified as pathogenic are not uniform; for while they generally assume a slender bacillary form with single terminal flagellum, the plump micrococoid and longer thread-like and irregular forms are to be found in some instances. Active motility seems to be an inherent characteristic, and among the physiologic functions that of coagulating milk is least variable. Gelatin is always liquefied by the members now included in the pyocyaneus group, although the rate of liquefaction differs. Indol is not produced by all the races, and none of them is known to ferment the sugars. Some reduce the nitrates to nitrites. The chief physiologic characteristic of this group of bacilli, and the one by which they are best known, is the property of producing fluorescence and pigments. The pigments elaborated during the active growth of the bacilli in culture media are readily differentiated by physical and chemical tests; sometimes only the fluorescent pigments are formed, sometimes only pyocyanin, more often both. It has recently been proposed to classify the members of this group according to the variations in pigment production. The property of forming fluorescence and pigments is often lost in cultures kept under artificial conditions, and, of the two, that of

forming pyocyanin first disappears. The behavior of pyocyanus on potato, differs widely in cultures from various sources, probably in keeping with the variations in pigment-forming. Whether the nonchromogenic bacilli, now associated with this group on general morphologic and biologic grounds, have suffered loss or suppression of a former pigment-forming capacity is not certain, though from what is seen under artificial conditions it is quite probable that they are varieties.

Morbid Effects ; Toxins ; Agglutination.—These bacilli were first found in the blue or green pus of wounds or the pigmented bandages soaked with wound secretions, the color in both cases being elaborated by the pyocyanus bacilli. In wound infections these bacilli are sometimes found, usually mixed with the commoner pus micro-organisms. They have also been found in various other local pathologic conditions, some of which apparently were solely due to their pathogenic activities. Thus they appear in purulent middle-ear disease, in suppuration in the cranial sinuses and meninges, in angina, bronchitis, bronchopneumonia, pleurisy, pericarditis and endocarditis, esophagitis, enteritis, metritis, appendicitis and peritonitis, synovitis, ureteritis, and pyelonephritis. A form of septicemia, sometimes with hemorrhages and with peculiar vesicular, papular, or bullous skin eruptions, also follows infection with this organism. Besides these more acute forms of infection, there is evidence to show that chronic infections and intoxications may also be induced by these bacilli. From the array of acute diseases above cited, it is evident that inflammation and suppuration are a frequent consequence of local pyocyanus infection. In the mucosa of the alimentary tract, inflammation may also be induced, with swelling of the lymphoid follicles, submucous hemorrhages, and finally necrosis of various stages, from superficial erosion to deep ulceration. Pyocyanus ulcers, situated as they frequently are in the lower ileum and accompanied by swelling or even suppuration of the contiguous mesenteric nodes, present an anatomic picture closely simulating typhoid fever. Hemorrhagic inflammation and necrosis are also produced in the mucosa of the genito-urinary tract. In the acute general pyocyanus infections the lesions are splenic tumor, with the usual macroscopic evidences of congestion, and parenchymatous degeneration of the other viscera. Microscopically, parenchymatous lesions of the heart, liver, spleen, and kidneys, focal hemorrhages, and focal necroses, especially in the liver, are encountered. Chronic pyocyanus intoxication exerts its deleterious effect principally on the central nervous system, and experimental reproduction of this affection results in the formation of hemorrhagic foci in various parts of the brain, together with myelitis and neuritis.

Experimental inoculation of laboratory animals varies considerably in its results, according to the virulence of the particular race of pyocyanus bacilli employed. In successful cases subcutaneous injections of fresh cultures in guinea-pigs or rabbits produce spreading edema, inflammation, and suppuration, followed by general infection and death ; intraperitoneal injections are more rapidly and certainly fatal, generally causing suppurative peritonitis.

Clinical evidence in the case of human beings, and experimental studies, point to the action of a toxin to explain the phenomena of pyocyanus infection. This toxin has not been definitely isolated, but appears to be intimately united with the bacterial cell. Injections of the bacilli killed by appropriate means cause intoxication in susceptible animals, and by

graduated dosage an immunity may be induced. The blood-serum of such immunized animals possesses active agglutinating properties when brought in contact with fluid suspensions of motile bacilli. The blood-serum of spontaneously infected human beings also produces agglutination, although the reaction is still too uncertain for clinical application. Antitoxic substances are produced in the blood-serum of pyocyanus-immune animals, and such an antipyocyanic serum has been advised for practical therapeutic use.

The Bacillus of Influenza.—Richard Pfeiffer's announcement in 1893 of the discovery of the specific exciting agent in influenza, and the thorough studies recorded in his report, have been generally credited, and little disposition is manifested at the present time to doubt the correctness of his conclusions, although here again we have a case in which positive evidence from the standpoint of experimental reproduction of the typical disease has not been satisfactorily obtained. Pfeiffer's organism is a short, plump bacillus, found chiefly in the purulent secretion from the respiratory tract in influenza. It grows sluggishly in the laboratory, requiring a special

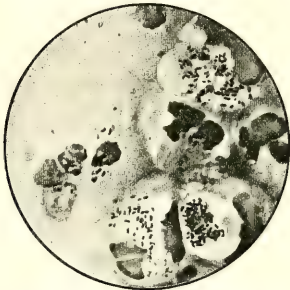


FIG. 85.—Bacillus of influenza: cover-glass preparation of sputum from a case of influenza, showing the bacilli in leukocytes; highly magnified (Pfeiffer).

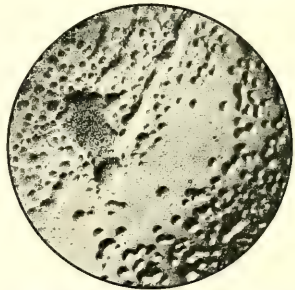


FIG. 86.—Bacillus of influenza: colonies on blood agar-agar; low magnifying power (Pfeiffer).

culture soil, prepared by smearing sterile blood or semen on the surface of ordinary nutrient agar. Upon yolk of egg, cultures may also be obtained. The influenza bacillus is not subject to a wide range of morphologic variation; and the restricted character of the artificial media upon which it grows, and its early death upon these media, make it difficult to determine its physiologic characteristics and variations. It must quickly find its way from one warm-blooded host to another, or perish; and the opinion is generally accepted that influenza is directly contagious through the medium of the infected respiratory discharges. Possibly an intermediate animal host may serve to harbor the bacterium and to transmit it to the human being, although no positive evidence in support of this assumption has been obtained. The difficulty of producing infection in the laboratory mammals by inoculating them in various ways with influenza cultures is also against this view. By resorting to intracerebral injections of living bacteria, Cantani has lately succeeded in producing a fatal form of influenza in rabbits, with marked symptoms of nervous irritability; and, contrary to the usual result of inoculations, the specific bacteria were found not only increased in

the local seat of infection, but present in the circulating blood and in remote organs, both microscopically and by cultures. About the injection-site was a gelatinous edema with numerous bacilli, the meninges were hyperemic and contained a serohemorrhagic transudate, the brain-substance was injected, and in the ventricles there was a purulent exudate. The peritoneal cavity contained an inflammatory exudate, the spleen was swollen, the adrenals and lungs congested, the liver hyperemic and in a state of fatty degeneration, and the kidneys well advanced in parenchymatous change. But in general the effects produced in man by this organism are such as to suggest an intoxication rather than a generalized infection.

Morbid Effects ; Toxic Products ; Immunity.—The principal anatomic alterations of influenza are found in the respiratory tract, a hyperemia and inflammatory reaction of the mucosa appearing in the larynx, trachea, and bronchi. Of especial significance is the pneumonia, which is the most frequent complication of influenza. This may take the type of a lobar or croupous pneumonia with an abundant fibrinous exudate, quite like the lobar pneumonia following a pneumococcus infection. In other cases the exudate is poor in fibrin and richly cellular, and accessory foci of lobular pneumonia are to be found with the lobar affection. The purely catarrhal or lobular form of pneumonia is also frequent. It is not rare for the acute pulmonary process to be followed by an interstitial, indurative inflammation taking a chronic course. Pleuritis, especially of a fibrinous character, often complicates the pneumonia ; and abscess, localized necrosis, and extensive gangrene are not infrequent terminations. As marking the systemic effect of the infection, a swollen spleen is commonly encountered. Generally the kidneys and bowels show little evidence of disease, though there is a so-called "intestinal" influenza running a clinical course somewhat like typhoid fever and marked by a catarrh of the intestines and an enlarged spleen. Among the serous membranes attacked are the cerebral and spinal meninges, and the inflammation may take a serous, seropurulent, or suppurative form. The pleura, pericardium, and even the endocardium are liable to infection from the organism of influenza. The nasal and pharyngeal mucosa are often involved, from which such complications as middle-ear disease and sinus inflammations sometimes follow. Secondary or mixed infections with other pathogenic micro-organisms at times complicate the course of pulmonary influenza, and tuberculosis is not rarely a terminal consequence of this disease.

That an intoxication of some sort must result from the localized action of the influenza bacterium on the respiratory mucosa seems highly probable from the natural history of the infection in man, where such symptoms as profound weakness and evidences of nervous exhaustion appear, quite out of keeping with the local lesions. It appears, in fact, that the poison produced in consequence of influenza has a selective effect on the central nervous system, both from the preponderance of symptoms pointing to disturbance in the brain and spinal cord, and from the results of intracerebral injections of cultures of the influenza bacterium. Both living and dead micro-organisms produce symptoms of experimental toxemia in the nervous system, which has led Pfeiffer to conclude that the specific toxin is closely combined with the protoplasm of the bacterial cell. Attempts to isolate the influenza poison have thus far been negative.

In influenza there is little to be hoped for in the way of an artificial or

passive immunity. A previous attack of the disease confers but a transient immunity or none at all. Certain individuals are evidently strongly predisposed to the infection, while others enjoy a partial or complete immunity. Efforts to induce experimental immunity in laboratory animals have also been of little avail, and no one has succeeded in producing a protective or curative serum for influenza.

The Bacillus of Plague.—It is conceded with remarkable unanimity that the bacillus discovered by Yersin and Kitasato in 1894 (*Bacillus pestis*) is the causative agent of plague in all its forms. The organism is a rather thick bacillus, appearing usually as a short, plump rod. Its morphologic variation is not extensive, if we except the irregular and even branching forms produced on saline agar; while motility, noncharacteristic growth on ordinary media, negative proteolytic function, and active pathogenicity are remarkably constant attributes in bacilli from various sources and different parts of the world. It is the last-named attribute, pathogenicity, that especially marks the pest bacillus as a specific micro-organism.

Bubonic plague is essentially a disease of filth and poor hygiene. The specific bacillus often, if not invariably, chooses the rat (and possibly the mouse) as an intermediate host, infection being carried from rat to rat, and from rat to man under similar unsanitary conditions. It is further suspected that another animal of uncleanly surroundings, the flea, may transport the bacilli from rat to rat, and from rats to human beings. While this method of transfer is by no means improbable, the facts that the urine and feces of plague-stricken rats contain the bacilli, and that the dead bodies of infected rats also swarm with the organism, seem well-nigh sufficient to explain the spread of the disease. Flies also, perhaps, carry the bacilli. The appearance of the disease in the rodents before and during epidemics among human beings has been repeatedly confirmed, and it seems reasonable to credit the distribution of the malady primarily to the rat. But little has been ascertained as to the purely saprophytic habits of the pest bacillus, although it is claimed that organisms similar to it have been found in the soil.

Uncleanly habits and careless exposure of the skin to infection account for the majority of cases of bubonic plague in man. The bare feet and legs of male natives in India, China, and other eastern countries where plague is epidemic offer a ready portal for entry of the bacillus, and in women the unprotected hands and arms. Although the skin marks the point of introduction of the disease in most cases, inhalation infection occurs, and infection by swallowing is by some considered possible. All of these routes may be successfully employed in experimental plague, particularly in the rat, which may be infected by feeding it with the flesh of diseased animals or by cultures introduced in various ways.

Morbid Effects.—Human beings spontaneously infected with plague show one of three types of the disease: the bubonic, pneumonic, or septicemic. In the majority of cases the bubonic type develops, characterized in the severe form, as its name indicates, by buboes or swollen and discharging lymph-nodes. Here the infection atrium is generally the skin, in which a local lesion like a carbuncle may mark the exact spot of first attack. From the point of entrance in the skin the infection travels to the surrounding region, which responds by rapid swelling and sometimes by hemorrhagic edema of the connective tissues. From the group of glands first attacked the disease spreads to other superficial nodes, so that the glands of the entire

body, both superficial and deep (including the bronchial and mesenteric nodes), often enlarge. In the superficial glands, especially those adjacent to the primary focus, softening and the discharge of a puriform fluid often occur. In the pneumonic type, as the name indicates, the chief gross lesion is a bronchopneumonia evidently due to aerial infection; while in the septicemic type the bacilli rapidly invade the blood from the primary focus, with only moderate involvement of the lymph-glands. There is a mild lymphatic variety of the plague; but except for this, taking any of the three types mentioned, the disease is generally fatal.

Aside from the swollen and often softened and necrotic superficial lymph-glands and the generally enlarged lymph-nodes, usually showing hemorrhagic foci on section, the morbid anatomy of plague is quite variable. Hemorrhagic ecchymoses in the skin, and submucous and subserous hemorrhagic areas are common. The spleen is swollen, soft, and contains macroscopic or microscopic hemorrhages. The kidneys show a moderate parenchymatous degeneration and are congested; the liver is somewhat swollen, and either pale or deeper red than normal. Hemorrhagic softening and superficial necrosis may be found in the stomach and intestines. Lobular pneumonia may be present, even in the bubonic type of the disease, and serofibrinous or purulent meningitis has been observed. In all the affected organs the pest bacilli are easily found, particularly in the blood-vessels.

Histologically the most important alterations are in the lymph-glands, in which the blood-vessels are found engorged with corpuscles and the cells increased in the earlier stages. Both lymphoid and large, clear hyaline cells appear in the affected node, the latter evidently being phagocytes, from the uniformity with which they are found with bacilli in their substance. An unusual number of mast-cells has been observed in the diseased glands. In more advanced stages, diffuse necrosis of the cellular elements of the gland occurs, until almost the whole gland-substance becomes converted into a mass of cellular and nuclear detritus with hordes of bacilli. Indeed, the larger bulk of some of these swollen and disintegrated glands may be made up of pest bacilli. Both the blood-channels and lymph-channels in and about the affected gland contain numerous bacilli, sometimes making bacterial thrombi of considerable size. It is significant to note that comparatively few polymorphonuclear leukocytes are to be found in the bubo, even when the disintegration is extreme, so that the process cannot properly be regarded as a suppuration, but as having more resemblance to the softening of a tuberculous focus. The pneumonia of plague seems to show no special variation from an ordinary bronchopneumonia, and the histologic changes in other viscera have nothing distinctive.

Toxic Products; Agglutination; Immunity.—From the rapid and extensive necrosis affecting the cellular elements of the pest bubo, it seems reasonable to conclude that the infecting bacilli produce a toxic substance especially destructive to the cells in their neighborhood. That this is not a

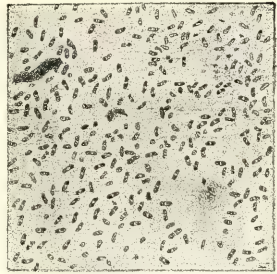


FIG. 87.—Bacillus of bubonic plague (Yersin).

diffusible toxin is probable from the absence of pronounced necrotic lesions in tissues and organs remote from the bacterial foci, though this must not be accepted as final, since some evidence seems to contradict it. However, no one has succeeded in separating a poison from the pest bacillus giving the specific effects of the living micro-organism, and it is therefore thought that the toxin, whatever its nature, is closely combined with the protoplasm of the bacterial cell, as is presumably the case with the organisms of typhoid fever and cholera.

A serum reaction may be obtained with fluid cultures of actively motile pest bacilli; but this agglutination test is unreliable for diagnostic purposes, both because of the difficulty in obtaining bacilli not already in clumps, and from the fact that only the serum of plague convalescents seems to contain the agglutinating substances.

It is claimed that a protective immunity of short duration may be produced in human beings by the injection of a vaccine consisting of a small dose of a fluid culture of the pest bacilli modified by heating to 70° C., and preserved by the addition of carbolic acid (Haffkine's prophylactic fluid). A serum said to possess specific antitoxic virtues has been prepared by injecting horses with increasing doses of living pest bacilli, and, while this antitoxic serum has no curative influence when the disease is established, its promoters assert that a small dose confers a protective immunity of some fifteen days' duration.

The Bacillus of Diphtheria.—There is no doubt that the so-called diphtheria bacillus of Klebs and Löffler is the specific cause of genuine diphtheria. Many of the clinical and pathologic features of the disease in man have been elucidated by laboratory experiments on animals. A special distinction pertaining to this micro-organism is that it has furnished a most brilliant and successful experimental demonstration of the mode by which it kills, and of a method of specific serum therapy applicable in medical practice.

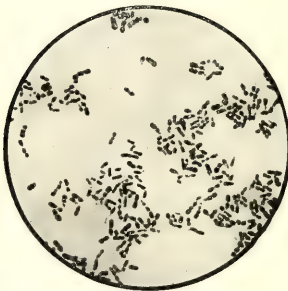


FIG. 88.—*Bacillus diphtheriae*, from a culture upon blood-serum. $\times 1000$ (Fränkel and Pfeiffer).

The shape and size of the organism of diphtheria is inconstant under varying conditions of natural and artificial growth. Sometimes it appears, both in the local lesion (the pseudomembrane in the throat) and on ordinary artificial culture media, as a short, plump rod. At other times it is long, straight or curved or bent, sometimes showing swollen, club-like, spindle-shaped, or even spheric ends. True dichotomy has also been noted, and several recent writers have removed the group of diphtheria organisms from the bacilli and have placed them among the branching, thread-like fungi. Bizarre branching forms appear both in sections of infected tissues and in cultures, being therefore no product of laboratory artifices, although the organism is susceptible to alterations in culture media, as shown by its property of producing shorter, thicker rods on glycerin agar than on Löffler's medium. Change from one animal species to another (guinea-pig to rat, for example) is capable

of altering the morphology strikingly. The physiologic characteristics, like the production of acid, the indol function, and the elaboration of toxic substances, are also variable. Hence a diversity in pathogenic action of these bacteria might be expected, and no doubt the failure to make allowance for these morphologic and physiologic variations has created many examples of the so-called "pseudodiphtheria bacilli."

To fix upon one characteristic as unalterable is difficult ; while recognizing the practical usefulness of special differential culture methods and of specific staining methods, like Roux's or Neisser's, in differentiating the true diphtheria organism from the pseudobacillus, the xerosis bacillus, etc., these reactions must not be regarded as specific in a biologic sense. The same may be said of the laboratory test for pathogenicity.

Morbid Effects.—The initial lesion wrought in man by the micro-organism of diphtheria is almost invariably an intense local inflammation, quickly followed by a membranous deposit. The favorite point of attack is the throat. We know nothing of the conditions that underlie such an attack, for a bacillus which laboratory tests show to be extremely virulent may reside on the pharyngeal mucous membranes of an entirely healthy person or produce only a slight local inflammation. Other and apparently less virulent examples may produce a rapidly fatal affection. Constitutional differences in the host are doubtless factors of great importance in determining the susceptibility to and effect of diphtheria, as is seen in the unfavorable prognosis of the malady and the inefficiency of specific serum treatment in victims having the lymphatic constitution. Previous or simultaneous infection with other pathogenic organisms is doubtless also an important matter. From these and other undetermined conditions a good deal of difference is shown, both in the local and systemic effect of diphtheria.

The manner of transportation of the infecting organism from host to host is not entirely clear ; for while much evidence points to direct transportation, other cases appear anomalous. How the organism passes its saprophytic existence is not known, although some observers have directed attention to milk, water, and even to flowers and plants, as intermediate carriers of diphtheria. Household pets, like cats and birds, occasionally harbor the diphtheria bacillus.

Aside from the throat and nose, the primary infection in diphtheria may occur in the mucous membrane of the eyes or of the genitals and in wounds of the skin. It is possible, too, that the organism may now and then gain access to the lungs, heart, or circulating blood, without the presence of a demonstrable external diphtheric lesion.

Its fibrinous structure is the most prominent characteristic of the localized diphtheric lesion. Following the inflammatory edema which ushers in the infection, comes the exudate or membrane which covers the mucosa more or less thickly. This membrane is white or grayish ; when sectioned, and examined with low powers in the fresh state, it shows several distinct layers : an outer grayish turbid one, a middle white glistening one, and an inner dark layer. All these zones are composed principally of fibrin in various states of aggregation, the central zone being compact, with less of the fibrillary components, and its glistening is due to a hyaline transformation to which the diphtheric exudate is particularly prone. Examined with high powers, and particularly after special staining for fibrin, the tangled threads

are seen making a network and becoming aggregated into more or less confluent masses or plates in the middle layer. Chinks or spaces are everywhere present in the membrane, although less abundant in the middle layer. Cells also abound in the fibrinous exudate, varying in different cases and in different stages in the same case; some present normal outlines, others show necrosis often reaching a stage in which only nuclei or nuclear fragments or chromatin dust remains. The early cellular elements are chiefly polynuclear leukocytes, afterward followed by mononuclear lymphocytes, and, in the deeper layers, by proliferated fixed-tissue cells. The behavior of the epithelial layer of the mucosa varies, sometimes remaining well preserved, again becoming disintegrated and contributing varying amounts of material to the membrane in the form of cast-off epithelial cells or aggregations of these cells. Fibrinous transformation may take place in the depths of the mucosa. The blood-vessels in the region are not only deeply injected, but often contain fibrinous thrombi. Curiously the lymphoid follicles of the infected mucous membrane seem to suffer little damage. In the superficial clear bounding layer of the membrane the diphtheria bacilli are found, often mixed with other bacteria.

In severe cases of the disease, most significant changes occur in regions remote from the primary seat; and while the specific micro-organisms may occasionally be transported by the circulation or find their way along the respiratory mucosa to the pulmonary parenchyma, still the deeper lesions cannot be ascribed to outwandering bacteria, but to the absorption of poisonous products generated *in situ* as a consequence of the original infection. In the more severe cases, the results of systemic affection are readily apparent in such anatomic changes as cloudy swelling and even fatty changes of organs, like the spleen, kidneys, heart, liver, and adrenals. More chronic cases of postdiphtheric intoxication show degeneration of the peripheral nerves; and, in both acute and chronic fatal diphtheria, changes in the ganglion-cells may be demonstrated by the Nissl method. While the faucial lymphoid follicles escape serious disturbance in the diphtheric process, more remote lymphatic glands are not so fortunate, as shown by the early swelling and uniform involvement in the cervical and other regions, and in the spleen. Histologically this swelling is accounted for largely by the presence of collections of endothelioid cells with large, oval, vesicular nuclei and a distinct nucleolus. These cells often occur in considerable areas in the splenic and intestinal lymph-follicles and mesenteric lymph-nodes. Many of them are hyaline, others well advanced in necrotic alterations. Inclusions of various kinds, like granules of necrotic protoplasm or of nuclear substance, or pigmentary masses giving the hemosiderin reaction, also appear in these large cells as the result of their phagocytic activity. But besides these lesions, diphtheria gives rise to a series of changes which, while by no means specific, are peculiarly the result of a general toxemia. These are the so-called *focal* or *insular necroses* which appear in the lymph-glands and certain viscera, the characteristics of which in diphtheria have been studied especially by Welch and Flexner. It is now known that these islands of necrosis occur in a number of different spontaneous infections, and that they may be experimentally reproduced by the injection of living bacteria and the poisonous products of bacterial activity, by the poisons of certain higher plants, the venom of poisonous serpents, foreign blood-serum, as the results of superficial burns, etc. The lesions may be reproduced in a typical manner in

animals by the injection of the poisonous products or toxins of the diphtheria bacillus.

Focal necrosis has been already described under *Necrosis* (see page 74), and its histologic features need not again be detailed; but it should be known that the mechanism of its production is not fully understood. Why, for example, the toxin should escape from the blood-vessels only in particular regions is not clear. In some instances the lesion can be shown, as Klebs has maintained, to be a minute infarction following the thrombotic or embolic occlusion of small blood-vessels. That such a process may occur in diphtheria is probable, since fibrinous metamorphosis is so pronounced a characteristic in the local infection and fibrinous thrombi are demonstrable in the blood-vessels of the pharyngeal mucosa and in more remote situations, especially in the blood-vessels and sinuses of the cervical lymph-glands, in the follicles of which deposits of fibrin also appear. The diphtheria toxin (and perhaps the other toxins concerned in focal necrosis) seems to have a peculiar property of elaborating fibrin-ferment, and the presence of this ferment in the circulation may be an important factor in favoring microscopic thrombosis and infarction. On the other hand, some of the foci are probably local tissue-reactions against the diffused toxin.

Diphtheria Antitoxin.—A temporary active immunity may be secured in susceptible animals by inoculation with living diphtheria bacilli at first attenuated by one of several methods, and later used in full virulence. But such a process is dangerous, unreliable, and unnecessary, since a more certain immunity may be secured by the use of the bacteria-free poisonous products of their growth, the *diphtheria toxin*, the chemical nature of which is not yet understood. In susceptible animals immunized by means of gradually increased doses of diphtheria toxin, an antidotal substance or antitoxin makes its appearance, chiefly in the blood-serum, which has the property of conferring a temporary immunity against diphtheria or of arresting the progress of the disease in the earlier stages. As to the nature of this antitoxin, we know nothing positive—it is not desirable to discuss here the elaborate theories advanced to account for it and to explain the *modus operandi* of its protective and curative action; but in diphtheria antitoxin we possess a therapeutic agent of great practical value. In actual practice this remedy is prepared from horse's serum, the animal having been immunized by increasing doses of a diphtheria toxin obtained by growing virulent bacilli in special bouillon until the height of toxin-production, when the organisms are filtered out, the filtrate being the toxin. The testing of the potency of the toxin by graduated dosage in guinea-pigs, and the testing of the antitoxic serum to determine its relative toxin-annulling property (described in *antitoxin units*) in the same animals, is one of the most interesting demonstrations of the biologic laboratory, giving much the same satisfaction as mathematic or physical elucidations.

The Organism of Human Tuberculosis.—Koch's bacillus of tuberculosis is a parasite which through evolution has practically reached the state of obligate parasitism. That it is a product of the evolution of a once saprophytic micro-organism may be surmised from what we know of other less advanced pathogenic species which are daily met in both saprophytic and parasitic existence. Quite recently additional evidence on this point has been obtained from two sources. By compelling the human tubercle bacillus to live for a time in the body of certain amphibia and also by

long-continued growth on modified artificial media, its biologic characters have been so changed as to permit its cultivation on ordinary culture media at the ordinary room temperature, and at a rate of growth considerably in excess of that seen in the unmodified organism grown on special media at the thermostat temperature. That is to say, it is possible by this artificial means to restore to this highly developed parasitic species certain of the more hardy characteristics, which probably were lost through long adaptation to a parasitic existence in warm-blooded animals. Confirmation also comes through the discovery of a series of bacterial organisms morphologically allied to the tubercle bacillus, but departing from it in sundry physiologic characters. To this class belong the butter bacilli of Rabinowitch and others, the timothy, dung, and grass bacilli of Möller, and the bacillus from the crypts of the tonsils, described by Marzinowsky. Possibly, too, the bacilli of avian and bovine tuberculosis are distinct species, although their

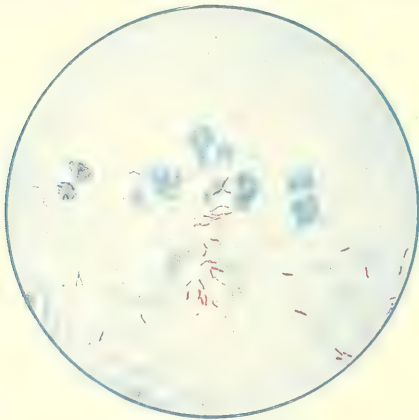


FIG. 89.—*Bacillus tuberculosis* in sputum, stained with carbolic fuchsin and aqueous methylene blue. $\times 1000$.

close morphologic and physiologic resemblance makes it probable that they are but varieties of the same group to which the typical bacillus of mammalian tuberculosis belongs.

In shape the bacillus is a slender rod, slightly curved, growing slowly at or near a temperature of 37.5°C ., and requiring special media for its artificial propagation. It reproduces in susceptible mammals a pathologic process running a definite course, with certain peculiar gross and minute lesions, closely resembling the tuberculous disease seen in man.

As to its morphology, the principal interest now hinges about the question of branching in the tubercle bacillus. There are those who claim that all branching forms of bacteria found in or obtained from tuberculous lesions or material, resembling Koch's bacillus in tinctorial and cultural peculiarities, are to be separately classed, and that the typical organism never shows dichotomy. But by experimental efforts, such as the intra-arterial or subdural injection of nonbranching tubercle bacilli, branching forms have been

produced. This evidence, taken with the intimate approach to the typical physiologic conditions of those branching forms spontaneously encountered in human tuberculosis, makes it highly probable that dichotomy is one of the characteristics of the tubercle-bacillus family, only temporarily lost in the most highly differentiated members. This phenomenon, which may be looked upon as a reversion, is also encountered in certain members of the tubercle-bacillus group growing spontaneously in the human organism, as shown at times in sections of tuberculous organs or in tuberculous sputum. Both under natural and experimental conditions, the tubercle bacillus sometimes goes beyond the condition of simple dichotomy to the formation of threads, thread-like masses, and radially arranged groups with clubbed ends, making an organism the morphology of which is similar to that of the ray fungi, as seen in actinomycosis. Indeed, from such morphologic and physiologic considerations as have been here outlined, systematic writers now generally incline to place the bacillus of human tuberculosis in the family of ray fungi of which actinomyces is the type, with affinities suggesting relationship both to the bacteria and to the moulds. In this light, the name bacillus as given to the organism of human tuberculosis is misapplied, although it seems expedient to retain it until the exact botanic position of it and its allies is better determined.

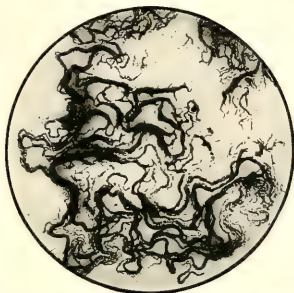


FIG. 90.—*Bacillus tuberculosis*: cover-glass preparation from a fourteen-day-old blood-serum culture. $\times 100$ (Fränkel and Pfeiffer).

A practical point of considerable importance concerns the staining peculiarities of the tubercle bacillus and its related forms. The well-known acid-proof and alcohol-resisting property of this organism, when stained by certain anilin dyes according to the method of Ehrlich and Koch and its modifications, can no longer be regarded as specific for the typical tubercle bacillus, for such organisms as the butter, timothy, tonsillar, and grass bacilli give identical tinctorial reactions; and even the differentiation by staining reactions of the smegma bacillus, the so-called syphilis bacillus, and leprosy bacillus is far from satisfactory. There seems to be a large group of bacteria, including those just mentioned, into the composition of which fat-like substances enter, rendering them resistant to acids and alcohol after coloration with certain anilin dyes, and the bacillus of human tuberculosis is only one member of this group. This consideration must of course affect our interpretation of such a diagnostic measure as the staining for the tubercle bacillus in sputum, exudates, and tissues, although, as we shall see, some of the less characteristic members of the tubercle-bacillus group simulate the typical tubercle-bacillus, even to the extent of producing a disease the pathologic features of which are much like those of genuine tuberculosis. At any rate, this evidence all goes to strengthen the theory of the former saprophytism of the typical tubercle bacillus, at the same time indicating the possibility that some forms of tuberculous disease may be caused by organisms of this group, which are still capable of saprophytic existence.

Morbid Effects.—The reaction of the human organism to infection with

the bacillus of tuberculosis presents a tolerably uniform picture. The principal lesion, and the one through which the name of the disease was assigned long in advance of the discovery of the specific parasite, is the familiar, translucent, grayish, millet-seed-sized nodule, the *tubercle*. As presented in miliary eruptions on freshly invaded surfaces, the macroscopic appearance of the tubercle is quite distinctive. In more ancient lesions, or in those in which extensive coalescence and exudation have occurred, the anatomic picture is less characteristic, although careful examination will usually disclose the individual tubercles. Anatomically, all gradations of the disease are to be seen, from the discrete, widely scattered miliary tubercles to immense degenerating pyogenic sacs representing destroyed areas. The gross picture varies not only according to the chronicity of the disease and the associated infections, but also according to the organ or tissues involved, there being marked difference in the behavior of cutaneous, osseous, lymphadenoid, serous, pulmonary, and cerebral tuberculosis, for example. The favorable outcome of a tuberculous process in the form of latent calcified foci, indurated foci, and even by connective-tissue repair, is a common sight at autopsy.

Histologically, tuberculosis is most often manifested by the collection of newly formed cellular elements constituting the tubercle, although it is important to recall that a diffuse cellular proliferation or a cellulofibrinous exudate may also mark the site of a tuberculous infection, with no histologic evidence of the tubercle proper. Following the usual description, the cellular elements of the tubercle may be divided into three classes: the *giant cells*, the *endothelioid* or *epithelioid cells*, and the *lymphocytes*. A reticulum, to some extent suggesting that of a lymph-gland, is at times present, and fibrin may also be found mingled with the cells. In early tubercles the blood-vascular channels are present, but their endothelial elements are soon stimulated into proliferative activity, and as the tubercle advances, especially in the more chronic and diffuse processes, the blood-vessels become occluded from endovascular inflammatory reactions or by thrombosis, this plugging of the vessels constituting one of the factors leading to the termination of tuberculous new formations—necrosis and caseation.

It was once thought that the giant cells of tuberculosis were peculiar to this disease, and that it was possible to distinguish tuberculosis by the peculiar features of the multinuclear cells of the tubercle. Such is not the case, since these cells offer no characteristic by which they may positively be distinguished from the giant cells of other granulomas, like syphilis, or from the foreign-body giant cells, whether under aseptic or infective conditions. The presence of demonstrable tubercle bacilli in the giant cells is distinctive, and possibly the calcareous or iron-containing masses thought by some observers to represent destroyed tubercle bacilli are also peculiar to this infection. The early necrosis of the giant cell of tuberculosis is suggestive, to be sure, but this outcome is by no means invariable. There is, indeed, a marked tendency to consider that this cell is not necrobiotic from its outset, the growing belief being that the giant cell is a defensive active product of tissue-reaction, and that it is phagocytic and reparative in function. The exact tissue-elements from which the giant cells arise—whether mesoblastic or epiblastic, or both—is not determined; nor is the mode of formation, whether by coalescence of small cells or by nuclear division and growth,

definitely ascertained. Similarly, the fate of these structures in healed tuberculosis is not clear, although a separation into small living cells, as suggested by Hektoen, is probable.

In like manner the origin or source of the endothelioid and lymphoid cells of the tubercle is not well settled, although analogy points to the endothelioid cells as springing chiefly from the fixed mesodermic tissue-elements (endothelial and connective-tissue cells), and the lymphoid from the blood, lymph-nodes, and possibly from the lymph-spaces. Whether the lymphoid and endothelioid cells are in any way related is unknown, although by some they are regarded as developmental phases of a common cellular element. The lymphoid cells in recent tubercles are poor in protoplasm, like those found in early inflammatory conditions generally; but in the more chronic tuberculous lesions the plasma-cell appears, with its more abundant basophilic protoplasm, whether by metamorphosis of the lymphocyte or otherwise is undetermined. The mast-cell may also make its appearance in the connective tissue about chronic tuberculous lesions. Like the giant cell, the endothelioid and lymphoid cells of the tubercle are not specific of tissue-reaction to the tubercle bacillus. More careful histologic study is demonstrating the extensive formation of endothelioid cells, both diffuse and focal, in a number of infections, like typhoid fever, diphtheria, scarlet fever, and pneumonia, while the lymphoid cell is common to inflammations generally. A still closer resemblance to the simpler infections is seen in caseous tuberculous pneumonia, in which exudation is quite as marked as proliferation, in rare cases even taking the characteristics of an ordinary purulent exudation. The same may be said of the fibrinous exudation, the thrombosis, and the endarteritis sometimes occurring in tuberculosis. Moreover, the necrotic changes, ranging from cloudy swelling of the giant cell and microscopic focal necroses to advanced caseous metamorphosis, are the same as in other morbid conditions. Histologically, tuberculosis is not to be distinguished by the peculiarity of any of the elements of the tubercle, but especially by the arrangement of the several proliferative elements—giant cells, endothelioid and lymphoid cells—into a focus, the sum of which is the tubercle. As, however, our knowledge of pseudotuberculosis is increasing, and with further light on the bacteria allied to the bacillus of Koch, we find that none of these histologic criteria is sufficient to stamp the process as tuberculosis without the concomitant identification of the typical tubercle bacillus. Thus the bacilli from butter produce in the guinea-pig a morbid process running an identical course with experimental tuberculosis, accompanied with macroscopic tubercles, and differing only in its more exudative nature (polynuclear leukocytes, fibrin, etc.) and the absence of giant cells, though lymphoid and endothelioid cells are proliferated. The timothy, dung, and grass bacilli produce a miliary tuberculosis in guinea-pigs, with gross and microscopic resemblance to the disease produced by Koch's bacillus.

Infection by the typical organism of tuberculosis is, according to our present ideas, only possible through the direct route from host to host, without intermediate saprophytic existence. All experimental evidence indicates that the tubercle bacillus has a considerable longevity outside of the animal body, under certain conditions, but with no power to reproduce until again implanted in suitable living animals. In man the infection occurs most commonly through the respiratory tract, probably not so much by the

inhalation of dried tuberculous material, as was formerly imagined, as from the bacilli-laden mist expelled during the coughing of consumptives. The large proportion of latent tuberculous bronchial-gland infections revealed by careful postmortem analysis of these organs shows how common this mode of inhalation infection is. Sometimes the lower respiratory tracts are spared, the invasion taking place through the nasopharyngeal surfaces, by way of adenoid tissue, like the tonsils, to reach the cervical lymph-glands. Infections by the digestive tract anywhere from the esophagus to the rectum, by the genito-urinary tract, through the nipples, by traumatism through the skin, are also possible, though more rare; these regions, and especially the bowels, are more often subjected to secondary infection. How far milk and meat of tuberculous animals are to be held accountable for intestinal tuberculosis is an unsettled question. Probably we shall also learn that transmission of infective material by insects, such as flies, is an important agent in spreading tuberculosis.

From the primary focus, infective material may be transported by the lymph-channels, blood-vessels, and by contiguous surfaces like serous membranes. The swallowing of expectoration from tuberculous lungs, especially in children and feeble-minded adults, is a frequent cause of gastro-intestinal infection. Erosion into the blood-vessels, with direct penetration of material containing the tubercle bacillus, or the production of infected thrombi and subsequent embolism, should always be sought for in sudden generalized eruptions of miliary tubercles.

Toxic Products; Immunity; Agglutination.—The tubercle bacillus elaborates poisonous substances during its biologic activity, but their nature and the part they play in producing disease are little understood. Artificially a poisonous mixture, with the peculiar specific effect of causing a characteristic febrile reaction in tuberculous animals, may be obtained; this is the *tuberculin* of Koch and its various modifications. These products have not proved to be of so much practical value as therapeutic agents as once proclaimed, although their employment for diagnostic purposes is still in vogue with human beings and on a large and seemingly successful scale for detecting tuberculosis in cattle. Despite extensive patient efforts, a useful antitoxic serum for tuberculosis has not been produced.

By growing tubercle bacilli in suitable liquid media with regular agitation for prolonged periods, it seems possible finally to separate the individual organisms and to induce a kind of motility, presumably an exaggerated form of molecular motion. Such cultures are now employed in performing an agglutination or serum test, with results indicating its value as a diagnostic measure, although the technic is so complicated and the results so meager that the method can only be looked upon as in the stage of experimental evolution.

The Bacillus of Syphilis.—There is not sufficient evidence at hand definitely to pronounce the bacillus of Lustgarten the specific cause of syphilis, although a strong tendency in this direction is manifested by those who have most carefully studied the subject. Should it eventually be ascertained that this micro-organism is the exciting cause of syphilis, then we will have another example of a highly evolved parasite comparable with the bacillus of leprosy.

The organism in question, which has been repeatedly found in primary, secondary, and tertiary syphilitic lesions, bears a close morphologic resem-

blance to *Bacillus tuberculosis*. Moreover, it belongs to the acid-proof and alcohol-proof class of bacteria, its property of retaining anilin dyes after moderate application of acids and alcohol making it possible to differentiate it in syphilitic tissues and secretions. Both in its morphology and staining reaction, Lustgarten's bacillus resembles the smegma bacillus, and several authorities claim that the syphilis bacillus is in reality nothing more than the latter organism. Specific staining tests have been devised for identifying these two bacilli, depending principally on the feeble alcohol-resisting power of the smegma bacillus as compared with the rather weak acid-resisting tendency of the syphilis bacillus. More reliance should, however, be placed on cultivation experiments, since it has been found possible to grow the smegma bacillus on artificial media, which has not been accomplished with that of syphilis. Typical tubercle bacilli are more acid-resisting than Lustgarten's bacillus, and can also be cultivated and inoculated into animals for differential purposes; and the leprosy bacillus, which has some points of similarity, is much more abundant in the morbid tissues and resists the action of strong acids to a high degree.

The contagium of syphilis is transmitted directly from one human organism to another. There is no authentic instance of indirect or intermediate transmission, and repeated efforts to inoculate other mammals have failed (Ravenel), the reputed successful cases proving to be instances of tuberculous or septic infection and not analogous with syphilis as seen in man. There is abundant evidence of the direct infection of the fetus *in utero*, both through the male and female sexual elements at conception, or later through the mother.

Syphilitic infection manifests itself by primarily local and later a general tissue-reaction tending to assume much the same microscopic granulomatous structure seen in tuberculosis and leprosy. It is remarkable for the extreme variation presented in the gross anatomic lesions as to size, color, consistency, and extent. With Virchow, we may distinguish two forms of tissue-change, the inflammatory hyperplastic and the gummatous or neoplastic degenerative. At the point of entry of the specific irritant a localized proliferation of connective-tissue elements, lymphoid, endothelioid, and sometimes giant cells, takes place. Being confined to a limited area, these proliferated elements produce a firm or indurated condition characteristic of the *initial sclerosis* or *chancre*. Necrosis and liquefaction of the tightly packed cellular elements lead to ulceration of the central portion of the indurated area, producing the familiar hard chancre of syphilis. Both in the primary lesion and in the subsequent manifestations of the chronic inflammatory reaction of syphilis, the lymphoid cells gradually become replaced by numerous elements giving the staining reaction of plasma-cells, and later fibroblasts appear, particularly in regions where protective granulation-tissue is forming as a barrier to the progress of the specific affection or in the healing process. Here, in the chronic lesions, mast-cells are also abundant. Like other allied infections, syphilis seems to irritate principally the elements of the connective tissue, and in consequence we find in both early and later lesions a proliferation of endothelioid cells, small round (lymphoid) cells, and giant cells. As in most other infections, the endothelioid cells, giant cells, and certain migrated leukocytes engage in phagocytic activity in the effort to rid the body of noxious invaders or to remove the detritus of cellular necrosis.

A gradual degeneration of the more or less localized nodular gumma,

ending in necrosis and caseation, is seen in the tertiary lesion. How much of this necrotic process is to be charged to the direct destructive effects of a syphilitic poison and how much to circulatory disturbance is not clear, although the latter factor must play a prominent part, since obliterative changes are extremely common in the blood-vessels of syphilitics. Sometimes the syphilitic affection is manifested only by a fibrous-tissue overgrowth throughout an organ like the lung or liver.

Syphilis seems also to stand in relation to certain diseases of the nervous system, particularly posterior sclerosis (locomotor ataxia) and meningo-encephalitis (general paralysis of the insane). The changes in those diseases are not specific, and bear no resemblance to the ordinary syphilitic lesions; hence they are sometimes called *parasyphilitic* lesions.

The Bacillus of Leprosy.—If we are to judge from culture experiments, then the bacillus of leprosy, which has never been grown successfully on artificial media, is more markedly an obligative parasite than the bacillus of tuberculosis. Morphologically it resembles the latter, and, now that attention is being directed to the affinities of the tubercle bacillus with the ray fungi, it is pertinent to recall that Babes some time ago noted a branching and radial arrangement of the leprosy bacillus resembling that seen in actinomycosis. Another point of resemblance is the strong acid-resisting property of the stained leprosy bacillus, a property in which it surpasses the most pronounced examples of this group of bacteria. Nothing is known as to the life history of the organism outside its human host; even the question of its contagiousness is disputed, although a direct transfer by contagion seems highly probable in view of the advanced parasitic adaptation of the leprosy bacillus—if it be really the specific causative agent—a conclusion in which opinion is almost unanimous even in the face of negative experimental evidence.

The usual morbid process with which the leprosy bacilli are associated is a chronic proliferative reaction, producing a granuloma somewhat like that seen in tuberculosis, actinomycosis, syphilis, and glanders. Its course is generally more chronic than any of these infections, and this is the more surprising in view of the immense numbers of bacilli concerned in the

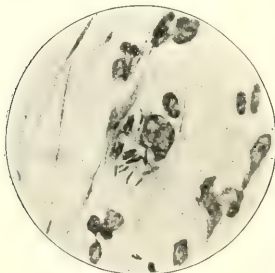


FIG. 91.—Leprosy bacilli in cutaneous cells.
× 1000 (Karg and Schmorl).

disease. The new tissue consists of richly cellular nodules or smaller foci with a fibrillary and vascular ground-substance. Most of the new cells are of an endothelioid nature, some being extremely large and at times vacuolated. Multinuclear giant cells also abound in the proliferated tissue. Vast numbers of the bacilli appear in the spaces of the leprosy granulation-tissue and also in the cells, sometimes lying in vacuoles, again crowding the cytoplasm so extensively as to leave no trace of cell or nuclear structure visible. Necrosis of the individual cells in the morbid tissue occurs, although the degeneration is slow in advancing to

the stage of liquefaction and ulceration. Caseation is rarely present, and, in several of the cases in which it has been reported, it has been shown by animal inoculation experiments to be due to mixed infection with the tubercle bacillus.

The leprous affection is for the most part found in the skin and subcutaneous tissues. The nerves are usually affected in combination with the cutaneous disease, a proliferative and indurative lesion resulting from the invasion of the bacilli. A more generalized affection is also noted, in which the mucous membranes, cartilage, lymph-glands, and such viscera as the brain and spinal cord, liver, spleen, and testicles, are invaded by the bacilli, with the production of more or less proliferative reaction, nodular or diffuse. Secondary affections due to other causes also develop; they are principally due to secondary infection with the bacillus of tuberculosis. But leprosy bacilli have been found in the circulating blood. The close morphologic and tinctorial resemblance between leprosy, tubercle, and smegma bacilli makes it always difficult to distinguish these organisms, especially when in combination, as they sometimes are in leprosy. Careful animal experimentation should decide definitely between tuberculosis and leprosy, since the latter disease has never been artificially communicated to any of the laboratory animals.

The Organism of Glanders.—While having its ordinary parasitic habitat in the Equidæ (horses and donkeys), the bacillus of glanders sometimes infects human beings, producing a morbid process similar to that seen in horses. The parasite is generally a small slender bacillus, growing on ordinary culture media, but without striking biologic characteristics. More careful recent studies of its morphologic characteristics have shown that the slender bacillary form is not the only one, for in agar cultures it has been found to produce extensive networks of tangled threads; and the individual elements, when separated, show wide variation in size and shape, while side-branching and sometimes multiple one-sided branching are observed, together with the development of clubbed ends and other asymmetric forms. These characters indicate the propriety of considering the micro-organism of glanders as allied to the ray fungi. The longevity varies considerably, some stocks dying in a short time under ordinary conditions of moisture and temperature, others surviving prolonged drying. True spores have not been identified, and, with the exception of irregularities in staining, probably due chiefly to plasmolysis, little change in form appears. In the affected equine and human tissues, the bacilli are usually abundant, lying in compact groups or diffusely scattered. Nothing has been determined as to the life history of these micro-organisms outside of the animal body, and the source of the extraneous infection is not known. Having once gained a parasitic foothold, transmission from animal to animal seems to be comparatively easy, since the chosen regions (nose and respiratory tract or skin) are those from which infection readily occurs through the breath or respiratory discharges. In the comparatively rare cases in which man contracts the disease, direct contact with infectious discharges or tissues and inhalation of infectious mist are considered to be the usual modes; and, in conse-

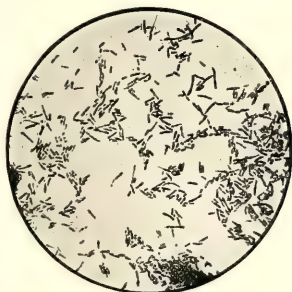


FIG. 92.—*Bacillus mallei*, from a culture upon glycerin agar-agar. $\times 1000$ (Fränkel and Pfeiffer).

quence, the starting-point is found in the conjunctiva, nasal mucosa, or the skin.

The effects of glanders infection in man are either acute or chronic. In the acute form the disease pursues a febrile course, like severe typhoid fever or a septic infection. In the cutaneous type a pustular eruption appears, the pustules discharging and leaving ulcers with dirty, ragged edges and purulent floors. A lymphangitis may proceed from the cutaneous foci, and an infiltration at times appears in the intermuscular connective tissue. Pulmonary embolic areas from the cutaneous lesions may occur, resembling pyemic foci, and the same process has been noted in the kidneys and myocardium. An aspiration-pneumonia of the lobular form at times follows glanders of the upper air-passages, the diseased areas remotely resembling tuberculous foci. They may terminate by softening and even by cavity-formation. The chronic form of human glanders is characterized by sluggish ulcers of the nasal, pharyngeal, tracheal, or bronchial mucosa, and by an induration of the cutaneous lesions. Abscesses may occur in the subcutaneous and intermuscular tissues, the exudate having a viscid, mucoid consistency. Caseous and even calcareous foci may also mark the site of chronic glanders, appearing in the lungs, bones, testes, and liver. The lymphatic glanders (farcy) seen in horses, or the more chronic nodular cutaneous farcy, is rare in man.

In the nasal mucosa the infection induces either a diffuse proliferation of lymphoid cells and endothelioid cells and migration of polynuclear leukocytes, or the proliferated cells may accumulate in groups, producing tubercle-like nodules. In the internal organs the process may be either a diffuse or a nodular one. The glanders lesions on the skin or mucous membranes tend to early necrosis, and the characteristic ulceration follows. In the viscera, necrosis is often accompanied by purulent infiltration and abscess-formation, or caseous metamorphosis ensues.

Straus's method of intravital diagnosis of glanders seems to give trustworthy practical results. It consists in the peritoneal inoculation of male guinea-pigs with suspensions of the suspected material (pus, infected tissues, etc.), a positive effect being marked by swelling of the testes as early as the second day, and by swelling and even ulceration of the scrotum by the sixth or seventh day. Autopsy shows the presence of glanders nodules in the spleen, omentum, and liver, and an inflammatory, purulent, and caseous infiltration of the tunica albuginea. A more elegant and useful method of diagnosis, of considerable practical utility in horses, is the *mallein test*, in which mallein (a glanders toxin obtained by growing glanders bacilli in fluid media and separating the organisms from their products by filtration) is injected into the susceptible animal, a positive effect being characterized, like that of the tuberculin test, by febrile reaction in four to ten hours and by edema at the site of injection.

While not capable of true motility, the bacilli of glanders, when separated in fluid cultures, possess a wide range of Brownian movement; and it has been found that agglutination may be produced by adding the blood-serum of infected horses to these fluid suspensions.

The Bacillus of Tetanus.—This sporogenic, anaerobic bacillus, identified in its saprophytic and laboratory characteristics by Nicolaier and Kitasato, is one of those pathogenic micro-organisms the causal relationship of which to the disease, tetanus, admits of exact experimental demonstration.

Abundant evidence shows that the bacillus ordinarily inhabits the superficial layers of the soil in company with several other pathogenic micro-organisms, and that it gains entrance to the human body or to that of a susceptible mammal either directly from the soil or from dirty objects. From the standpoint of parasitism, the bacillus of tetanus is a notable exception to the rule for pathogenic micro-organisms, being almost unadapted to multiply in the body of the host, and still capable of producing disease and almost certain death through the elaboration of an intensely virulent and rapidly diffusible poison. Its analogy is rather with the higher plants which elaborate poisonous products without being in any way parasitic, than with the class of parasitic micro-organisms to which it belongs. How such a poison-producing property should have been acquired in an organism not adapted to a parasitic existence is an interesting problem, only to be answered by a wider knowledge of the saprophytic life habits of the tetanus bacillus. In a state of Nature the organism is apparently a strict anaerobe; in its usual habitat, the soil, it fails to find oxygen-free conditions necessary for its vegetative existence, but it is provided with spores which, like those of the other anaerobic earth bacilli, are exceedingly resistant to ordinary destructive influences and have extraordinary longevity.

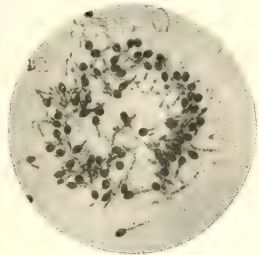


FIG. 93.—Bacillus of tetanus (spore-formation). $\times 1000$ (Migula).

Access to the human organism is gained almost exclusively through wounds; and the clinical types of traumatic tetanus, tetanus of the newborn and of the puerperium, are explained in this way. Doubtless, too, most examples of the so-called idiopathic or rheumatic form of tetanus depend upon the infection of minute and hidden or healed wounds. Possibly the stings of certain insects may also be found at times to be instrumental in carrying the infectious material. But under certain conditions of association or symbiosis with other bacteria it appears that the tetanus bacillus may assume aerobic functions, and under such circumstances it may multiply in regions supplied with oxygen. Some cases of tetanus complicated with pneumonia seem explicable on this basis; the tetanus bacillus, in association with the diplococcus of pneumonia, growing in the oxygenated pulmonary tissues. It is also noteworthy that the tetanus bacillus is commonly associated with one or another of the pyogenic bacteria in wounds from which tetanus is acquired; and since some of these wounds seem to offer no opportunity for anaerobic vegetation, it is quite possible that here also the symbiosis may aid the organism of tetanus in multiplying under otherwise unfavorable conditions. That the tetanus bacillus, isolated in purity and grown under artificial anaerobic conditions, reproduces tetanus in experimental animals is unquestionable; but by injecting pure tetanus cultures into animal tissues we are establishing conditions not present in spontaneous tetanus, particularly that coming from extensive superficial wounds where mixed infection is invariably present. At any rate, the clinical phenomena of tetanus are to be ascribed not to the extensive invasion of the organism with the tetanus bacillus, but to the poison set free by its local activity.

Morbid Effects.—Except for the local wound which pursues the course

common to such lesions, and the clinical manifestations of tetanus, which need not be here discussed, the reaction to this micro-organism and its poison is remarkably devoid of demonstrable gross or microscopic changes. From clinical phenomena it is evident that the central nervous system especially suffers from the effects of the tetanus poison, although even the histologic alterations here are slight. Careful examination of material from the cerebrum and especially the medulla of fatal cases of tetanus, freshly obtained and properly treated, shows changes in the ganglion-cells, such as disintegration of the chromophilic bodies and displacement of the nucleus, similar to those noted in other intoxications.

Toxin ; Immunity ; Serum-therapy.—Both at the point of inoculation in susceptible animals and in artificial media, the tetanus bacillus elaborates a poisonous substance believed to be a proteid—a toxalbumin. This poison permeates the artificial fluid media, and may be obtained in solution by filtering off the bacilli. By certain chemical manipulations it has been precipitated out of these solutions in a more or less pure state. The filtrate as well as the precipitate (tetanus toxin) is poisonous for susceptible animals in doses extraordinarily minute, and reproduces physiologic reactions corresponding precisely to the train of symptoms manifested by animals spontaneously infected with the tetanus bacillus. The injection of these poisonous substances in a form much attenuated (generally obtained by treating the fluid filtrate of artificially grown tetanus bacilli with some chemical or by heat) is tolerated by susceptible animals ; and, by gradually increasing the dose after suitable intervals, an immunity against the potent poison, either in its artificial condition or as elaborated by the living tetanus bacilli, may be produced. Just as in the case of natural tetanus, so in that produced artificially by the injection of bacteria or their toxins, a certain time elapses before symptoms manifest themselves. The shorter this “period of incubation” in the human subject, the more serious is the disease. The blood-serum of immunized animals becomes antitoxic ; that is, capable of neutralizing, in some manner as yet imperfectly understood, the poison of the tetanus bacillus. For practical therapeutic purposes, this antitoxic serum (tetanus antitoxin) is generally prepared from an immunized horse, and offered in the liquid or dry form. That it is an antidote to the tetanus toxin is undoubted from the positive results of numerous animal experiments ; but spontaneous tetanus as encountered in the human being has generally made such headway when discovered, and so much poison has already been elaborated, that therapeutic success after injection of the tetanus antitoxin is uncertain. Still, upon the whole, the results are such as to prompt the general employment of this method. As a preventive agent in case of suspicious wound infections, the use of tetanus antitoxin is rational, since animal experimentation proves that a passive protective immunity against tetanus may be secured by relatively small doses of the antitoxin.

As the tetanus toxin is eliminated in the urine, the injection of urine from a case of the disease into a susceptible animal, *e. g.*, a white mouse, may be used as a test.

Bacillus Aerogenes Capsulatus.—This is an anaerobic, pathogenic bacillus, ordinarily passing a saprophytic existence in the soil. It appears to be a constant inhabitant of the intestines of man and other mammals, possibly finding its way there along with certain uncooked green vegetables more or less covered with particles of earth, which form a part of human diet.

From its moderate variations in morphology, and more especially from the irregularity of its spore formation, together with slight physiologic variations in organisms from different sources, it appears that several varieties of allied bacilli are included in this group. Moreover, since the property of capsule formation is not possessed by some members of the group, which agree with the type species in other particulars, the name "capsulatus" can hardly be regarded as appropriate for all the varieties. Its most constant attribute seems to be the gas-producing one, hence the desirability of the term "gas bacillus," by which the organism is now commonly known, as applied by Welch and Nuttall, who first accurately described it.

Ordinarily the gas bacilli appear as rather coarse, nonmotile rods, resembling anthrax bacilli in size; they grow in clumps, in pairs and short chains, rarely in filaments. Spores are uncommon in bacilli from the animal body, and may or may not form on artificial culture media, of which blood-serum seems most suitable. They are anaerobic, though not so strongly as the tetanus bacillus. Glucose, saccharose, and lactose are fermented, hydrogen especially being evolved. Fresh tissues containing the bacilli, or freshly isolated cultures from infected tissues, are pathogenic for guinea-pigs, pigeons, sparrows, and rabbits, producing gaseous edema and necrosis which often spread rapidly. A useful test for the organisms of this group, devised by Welch and Nuttall, consists in the intravenous injection of the bacilli into rabbits, which are killed after a few minutes. Gas is produced in the blood and organs, where the gas bacilli multiply actively after the death of the animal, and whence they can be readily isolated.

Morbid Effects.—Cadaveric decomposition, accompanied by the production of gas in the body, may almost invariably be ascribed to bacilli of this group. The same is true of the formation of gas bubbles in the blood and of gas cysts in the viscera, particularly the liver. In both cases the gas bacilli probably find their way most frequently from the intestinal canal, which, as has been remarked, often harbors them in the living animal. Often gaseous blood and emphysematous organs (the "Schaumorgane" of the Germans) appear in autopsies one hour after death; but here, as in most if not all of these cases, the phenomenon is to be ascribed to an agonal invasion of the blood by gas bacilli, by which they are distributed to various organs and tissues, to multiply rapidly after death. On microscopic examination of the tissues a zone of disintegration is usually found around the clear.

During life, the most important condition ascribed to the pathogenic activity of this class of organism is emphysematous gangrene, a serious form of wound infection. Here the gas bacilli are principally concerned, obtaining access from the exterior through filth of various kinds. An exudate of a hemorrhagic, edematous nature, with comparatively few leukocytes, appears, with gas bubbles about which necrosis of the tissue-elements and mechanic disorganization may be observed. This gaseous and necrotic edema spreads, sometimes involving extensively the subcutaneous tissues of the body. Infections may proceed from other points, as the uterine cavity, urinary tract, gastro-intestinal canal, biliary apparatus, and respiratory tract. A general visceral emphysema with gas bubbles is often found after infection by the external or internal routes; but how much of this is to be assigned to agonal and postmortem production is difficult to decide. In some cases emboli of liver, spleen, and bone-marrow cells have been found in remote parts, like the lungs. In some of the fatal cases of emphysematous gan-

grene, death is apparently caused by the absorption of toxic products generated by the gas bacilli, although the frequency of mixed wound infections makes it difficult to eliminate other factors.

Little is known concerning the toxins produced by this group of anaerobic bacteria, and no substantial knowledge has been obtained relative to natural and artificial immunity.

The Bacillus of Malignant Edema.—Still another anaerobic, spore-producing bacillus inhabiting the soil and appearing as one of the agents of cadaveric decomposition, and occasionally of a morbid condition in man, is the so-called bacillus of malignant edema, described by the French, since Pasteur's announcement in 1877, as the "*Vibrio septique*." There is a strong family likeness between this organism and the gas bacillus of Welch and Nuttall, and most European bacteriologists seem to include with the bacillus of malignant edema all allied anaerobes, among them those that produce gas in the tissues. The laboratory differential points between the two organisms are a slight difference in morphology; with motility, general spore-formation, more rapid peptogenic power and putrefaction,

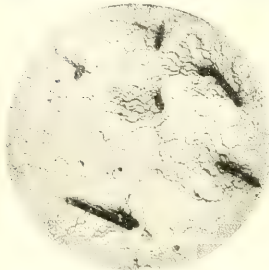


FIG. 94.—*Bacillus oedematis* (flagella).
× 1000 (Migula).

and lessened fermentative functions, as characteristics of the malignant edema bacillus. These features are hardly sufficient to be set up as specific, particularly since both organisms show considerable variation; and it seems highly probable that careful study will prove the bacillus of malignant edema and the gas bacillus to be simply varieties of a common anaerobic stock. The bacillus of malignant edema has been found in the intestinal canal of healthy animals.

The result of infection with this organism is a spreading bloody edema, appearing usually as a complication of wounds contaminated with dirt. Experimental malignant edema is readily produced in animals by subcutaneous inoculation with garden earth and similar material, showing that the usual saprophytic habitat of this organism is that common to the tetanus bacillus; indeed, a mixed infection of malignant edema and tetanus is at times seen in experimental cases and wound infections in man. Emphysematous gangrene and septicemia are also ascribed to the action of this organism, corresponding precisely to the effects produced by the gas bacillus, so that both the botanic position and pathologic bearings of the two bacilli are very confusing. Should specific differential characteristics be ultimately established between them, it is probable that the characteristic morbid effect will be found to be the absence of emphysema in the lesion produced by the malignant edema bacillus and its constant presence in organs and tissues invaded by the typical gas bacillus.

Bacillus Botulinus.—One of the indirect methods through which bacteria induce disease in animals is by the production of poisonous products in foodstuffs before these are ingested. Sometimes the foodstuff harbors both the living, active bacterium and the poisonous substances of its manufacture. The organism described as *Bacillus botulinus* is one of a group of anaerobic

bacilli, which act both directly and indirectly, producing in raw meat their toxic substances and also occasionally multiplying in the body of the infected individual.

This group of anaerobic bacilli somewhat resembles the malignant edema bacillus morphologically, although subject to considerable variation in size and shape; and it shows similar physiologic characteristics when subjected to the routine laboratory tests. They are motile, usually sporogenic, proteolytic, and gas-producing anaerobes. Thus far they have been found to induce disease only when contaminating uncooked or partly cooked meats; these meats show more or less evidence of putrefaction. The contamination is generally to be ascribed to prolonged sojourn of meat in dirty surroundings or to imperfect methods of preservation.

Morbid Effects.—The prominent symptoms of botulism in man are colic, vomiting, and diarrhea, usually followed by constipation. Evidences of profound disturbance of the nervous system, such as visual disorders and ptosis, appear in severe cases, followed by circulatory and respiratory irregularities, anuria or dysuria, aphonia, collapse, dyspneic attacks, and gradually weakening pulse in the fatal cases. Consciousness is intact almost to the last, delirium appearing only in the collapse. Drowsiness is often marked, and muscular palsies may appear. The gross changes at autopsy are not particularly prominent, a general visceral hyperemia and moderate parenchymatous degeneration, with punctiform hemorrhages in the brain, being most prominent. Microscopically the liver shows parenchymatous and fatty degeneration, with moderate emigration of leukocytes, while infarctions and fibrinous thrombi may be found in the kidneys, and a granular or fatty degeneration in the heart-muscle. The spleen is usually swollen and packed with red blood-cells, and phagocytosis may be abundant here as well as in the bone-marrow. In animals killed experimentally by contaminated meat or by the toxins of the bacilli, the changes above noted are found, together with a chromatolysis of the ganglion-cells in the nuclei of certain cranial nerves (hypoglossal, motor oculi, vagus) and of the Purkinje cells of the cerebellum. The blood-capillaries in these regions are choked, and hemorrhagic foci are frequent.

Poisonous Products; Immunity; Antitoxin.—Filtered infusions of contaminated meat, when administered by the mouth, produce the characteristic symptoms of intoxication in susceptible laboratory animals (guinea-pigs and rabbits), and these infusions are fatal for mice, pigeons, monkeys, and cats, when given subcutaneously. From liquid cultures of the bacillus a poisonous filtrate having similar effects may be obtained, and by adopting the measures usually practised to obtain bacterial poisons a toxin of extraordinary potency can be isolated from the cultures of the organism, the minimum fatal dose being considerably less than that of the tetanus toxin. Physically and chemically this substance has been found to resemble the toxins of diphtheria and tetanus; and, like these, it may be used in producing an artificial immunity in animals by properly graded doses. Protection against the poison as found in contaminated meat or as formed in culture media is eventually attained, and the blood-serum of these immunized animals is antitoxic, the antitoxin being a prophylactic and curative agent against the *botulismus bacillus* and its poisons.

The Organism of Asiatic Cholera.—This much-dreaded malady, having its home in India and occasionally visiting other parts of the torrid and

temperate zones in devastating epidemics, is associated with a micro-organism first thoroughly studied by Koch in 1884, and since generally regarded as the etiologic agent in cholera. It is called *Spirillum cholerae*, *Comma bacillus*, *Vibrio cholerae*, and is a rather small, slightly curved rod, often grouped so as to make distinct elongated spirils.



FIG. 95.—*Spirillum* of Asiatic cholera, from a bouillon culture three weeks old, showing long and degenerate forms. $\times 1000$ (Fränkel and Pfeiffer).

Under ordinary conditions of laboratory cultivation and as found in choleraic stools from different individuals, in different epidemics, and in various parts of the world, the morphologic variations presented by Koch's spirillum are insignificant; the only marked ones are the so-called degenerate or involution forms seen after growth for long periods on artificial culture media or in unfavorable surroundings. This morphologic constancy contributes an important element in the diagnosis of cholera, which has often been made by an examination of the suspected dejecta or surfaces soiled by dejecta.

The organism is motile and has terminal flagella; its growth on ordinary media is noncharacteristic; it does not ferment sugars, but has proteolytic power, liquefying gelatin and blood-serum. The ferments, bacteriotrypsin and invertin, are probably uniformly produced in favorable media, while labferment is not so regularly formed. Indol is formed in proteid media in large amount. During the first few hours or days of a new culture, nitrites are also produced, and the indol test may be performed by the addition of sulphuric acid alone, this constituting the well-known "cholera-red reaction" (nitroso-indol reaction). Some of the vibrios closely allied morphologically to the cholera vibrio, and organisms like the bacillus of diphtheria, likewise give this reaction. Physiologic variability has, however, been observed in spirilla obtained from cholera cases, such as difference in the rate of liquefaction of gelatin and blood-serum, absence of the nitroso-indol reaction, and negative pathogenic effects; but such deviations have generally been only temporary, and gradually disappeared under routine laboratory cultivation.

Notwithstanding the freedom with which the organism of cholera adapts itself to laboratory conditions, it seems to be well advanced toward obligate parasitism in the human being. At least, it is certain that all attempts to trace its life history outside of the human body have failed to show that it thrives in the saprophytic habitat imposed by natural conditions. Its longevity varies considerably, but, on the whole, is short, under the stress of external conditions. It has been repeatedly found alive in media like contaminated water and soil, and there is little question that through such means it has found its way from person to person. No evidence exists of its sojourn in an intermediate animal host by which it is propagated and distributed, but, like the organism of typhoid fever, it seems quite reasonable to believe that the agency of insects may be an important factor in favoring distribution, especially to human foodstuffs. But there is abundant proof that in the small intestine of the cholera patient the spirillum of Koch finds con-

ditions well suited to its vegetative existence. Even here, however, unfavorable factors, such as peculiar reactions of the intestinal contents, or that state which we are pleased to style "increased vital resistance," occasionally hamper the organism, particularly in its pathogenic tendencies, in witness of which we have the finding of cholera vibrios in the stools of seemingly healthy individuals in contact with epidemic cholera.

Morbid Effects.—The route by which cholera vibrios gain access to the human organism seems to be by the gastro-intestinal canal exclusively. Experiments on animals tend to show that the acidity of normal gastric juice has a harmful influence; and, in order to obtain positive effects from feeding-experiments, the gastric secretion is neutralized and intestinal peristalsis retarded by medicinal agents. Whether such a condition must precede spontaneous cholera infection in man, and, if so, how it is brought about, are not known.

Once having gained access, the morbid conditions excited by the spirillum manifest themselves primarily in the small intestine by an inflammatory reaction varying in extent and severity. There may be only a hyperemia, or the mucous membrane may be soft and edematous and studded with hemorrhagic ecchymoses. Inflammation with more or less swelling and superficial necrosis of the mucosa may appear, particularly in the lower ileum, and a swelling of the intestinal lymphoid follicles, both solitary and agminated, is a constant phenomenon. In more advanced cases of severe intestinal infection, diphtheric plaques may appear on the mucosa, and the necrosis may advance to the stage of ulceration, with considerable defects in the lining of the bowel. In all stages the intestine is filled either with the thin, rice-water, flocculent material so characteristic as a clinical evidence of the disease when discharged, or with a bloody, offensive fluid. In this fluid the vibrios are present almost unmixed; they also appear in the superficial epithelial cells of the mucosa, sometimes penetrating well into the submucous lining. Exfoliation of the superficial epithelium is quite constant, as a consequence of which these flakes containing spirilla are found in the stools. Of the other gross lesions, those shown in the kidneys are most marked; here well-pronounced parenchymatous degeneration is seen, and in certain cases the damage to the kidney is of high degree, while the intestinal alterations are slight (uremic form of cholera). In the liver, spleen, heart, lungs, and brain, the gross changes are those common to many acute infections, being more or less marked in different cases. However, even where the naked-eye evidences of visceral alterations are not pronounced in cholera, the disease may nevertheless have caused grave alterations; for precise histologic study shows here, as in the case of most other microbic affections, considerable disturbance. Thus it has recently been shown that in fatal cases of Asiatic cholera the hyperemia and punctate hemorrhages of the brain are accompanied by intense degenerative changes in the ganglion-cells—pigmentary atrophy, vacuolation, chromatolysis, and the immigration of leukocytes. The cells of the cerebral capillaries show fatty and granular degeneration also. In the abdominal viscera, degenerative and necrotic changes appear in the parenchyma, and an inflammatory reaction in the stroma. Focal necrosis is not uncommon, especially in the liver, and here the blood-vessels of the interlobular and intralobular tissues may contain thrombi, in some of which cells of the splenic pulp can be recognized, while free liver-cells appear in others. The splenic cells doubtless find their way here by the

portal route; and, while the presence of liver-cells has not been noted in the pulmonary vessels, their presence might be readily expected from the circulatory mechanism.¹ Insular necrosis in the liver of cholera cases sometimes at least may be ascribed to emboli of splenic cells. The formation of such emboli is probably the result of a toxemia, but the exact mechanism of the phenomenon is not known. In the case of cholera, however, such an intoxication or embolism must be held to account for lesions in parts of the body remote from the gastro-intestinal canal, since the spirilla are generally absent from the blood and organs in fatal cases.

Cholera Toxin; Immunity; Protective Vaccination.—That the fatal results of infection by the cholera vibrio were due to an intoxication was held by Koch in his early studies of the disease. From our present knowledge it appears that, like the typhoid bacillus, the organism of cholera elaborates both a soluble diffusible toxic substance and one intimately bound with the protoplasm of the bacterial cell. This latter poison, studied with especial care by Pfeiffer, is obtained by killing actively growing vibrios. Guinea-pigs, after intraperitoneal inoculation, react very promptly and with symptoms of collapse, such as are observed in the algid stage of cholera in man. With smaller doses a temporary intoxication and fall of temperature occur; and, after complete recovery (ten to fourteen days), living, virulent vibrios from recent cultures may be cautiously introduced in gradually increasing quantities at appropriate intervals until the usual reaction ceases. By this procedure an immunity is conferred, and the blood-serum of the immunized guinea-pig possesses several remarkable properties. Thus it produces rapid cessation of motility and clumping of living cholera vibrios (*agglutination reaction*), followed by a disintegration and solution of the bacterial cells (*bacteriolysis*) when mixed in proper proportions with the suspended organisms outside of the living body. This interesting phenomenon, first noted by Pfeiffer and more fully investigated by Gruber and Durham, prepared the way for the agglutination reaction as now applied to the diagnosis of several infectious diseases, especially typhoid fever, and for the opening of the new field of cellular reaction and cellular solution which is being extensively investigated at present. It was also found that a similar inhibiting and destructive effect could be produced by injecting the serum and living vibrios into the peritoneal sacs of living guinea-pigs. Furthermore, the blood-serum of human beings who have recently recovered from an attack of cholera also possesses these agglutinative and bacteriolytic properties. In bacteriologic diagnosis these observations found practical application, since the serum of naturally or artificially immunized animals exerted its specific effect only on the typical members of the cholera-spirillum group, but not on several cholera-like vibrios hitherto believed to be related to it or identical with it. For practical application in treating cholera in human beings, these experiments have thus far been unavailing, and the method of pro-

¹ Cellular emboli, composed of elements from the splenic pulp, bone-marrow, endothelioid cells originating in lymph-nodes, and even liver-cells, have lately been recognized in the course of careful histologic examinations as occurring in a number of acute infectious diseases—for example, diphtheria, scarlet fever, pneumonia, typhoid fever, gas bacillus infection—and also in eclampsia. The significance of this process is not yet clear; in some cases it must be looked upon as an occurrence of the death agony, at other times all appearances point to the formation of cellular emboli during life, when they may be an important factor in determining lesions of the viscera in which they lodge. Focal necrosis may thus be induced by these emboli when lodging in arterioles or capillaries, the necrotic focus being really a microscopic infarct.

tective vaccination introduced by Haffkine, consisting in the injection of attenuated cholera cultures in two doses of increasing strength, must still be regarded as an experimental stage, though not without hopeful prospects.

Besides the spirillum of Koch, a series of vibrios with similar morphologic, physiologic, and pathogenic properties have been described, among which it will be sufficient merely to mention the vibrio of Finkler and Prior, the *Vibrio tyrogenes* of Deneke, the *Vibrio Metschnikovii* of Gamaleia, and a series of cholera-like vibrios or water vibrios obtained from water-supplies by bacteriologists in various parts of the world. Notwithstanding their manifest affinities with the cholera spirillum, there is little disposition at the present time to displace the vibrio of Koch from its etiologic position.

The Spirillum of Relapsing Fever.—The spirochete of recurrent fever, first described by Obermeier, an assistant of Virchow's, in 1873, is placed among bacteria by general consent, although this disposition of the organism is founded on very limited knowledge, as nothing whatever is known of its history outside of the body of an infected animal, nor of its stages within the host. It is not impossible that the suspicion of Saccharoff concerning the protozoan (hematozoan) nature of this parasite is correct, and that the peculiar flexible and highly motile spirilla observed in the blood of relapsing-fever patients during the febrile paroxysm are only one stage in the life history of the organism. Possibly the round, refractive bodies seen especially in the spleen when the fever subsides, and the intracellular whorls of living spirilla in the splenic pulp, described by Metschnikoff, are further steps in the development of a sporozoan parasite. This much may be said, that all attempts to secure and cultivate this spirochete by bacteriologic devices have failed, and it is concluded that the organism either represents a bacterium that has reached an extraordinary degree of obligate parasitism, or that the spirilla represent a stage in the development of a protozoan organism which, like some others of its kind, does not admit of artificial cultivation by ordinary methods. Nothing is positively known concerning the mode by which recurrent fever is transmitted from person to person. Klebs some years ago suggested, from analogy with occasional cases of anthrax, that insects might be found to serve as vehicles; and this view has lately been revived, put to the experimental test, and strengthened by infecting monkeys with recurrent fever through the agency of bedbugs. The infection has also been transmitted to the human fetus *in utero*.

Obermeier's spirillum appears in the blood of relapsing-fever patients just before and during the attack of fever, subsiding in the interval. By means of the infected blood the disease has been inoculated from man to man, and man to monkeys. In the latter animal the spirillum has been found in the spleen, bone-marrow, lymph-glands, liver, and kidneys. Con-

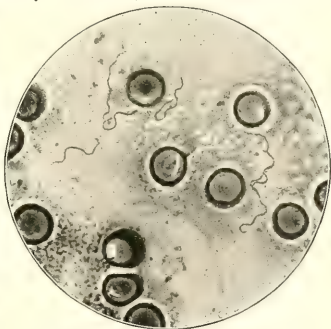


FIG. 96.—Spirillum of relapsing fever (Karg and Schmorl).

trary to Metschnikoff's assertions, splenectomy appears to have no marked influence on the progress of the infection. Phagocytosis, especially by leucocytes, is in active progress during the afebrile period, and the evidences of disintegration, which many spirilla show, result no doubt from the action of a bactericidal substance in the blood-serum, the nature of which has not been determined. But in the case of the spirochete septicemia in geese, which closely simulates relapsing fever in man, Gabritchewsky claims to have produced an immunizing and curative serum in the horse by intravenous injections of infected goose's serum.

The gross lesions of fatal relapsing fever are noncharacteristic, the swollen spleen and occasional parenchymatous nephritis being most marked. Careful histologic studies of the infected organs have not been reported. The blood during life may contain free melanin granules, and similar hematogenous pigment appears in the leukocytes during the afebrile period.

The Pyogenic Staphylococci.—Among the pathogenic spheric bacteria (*Micrococci*), those arranging themselves in grape-like clusters through division in various planes, and designated *Staphylococci*, are the best known. For the last twenty years, micro-organisms of this kind have been recognized as bearing some relation to suppurative lesions in man and other animals; and since the precise investigations by Ogston in 1881, and Rosenbach, Krause, Passet, and others in 1883–84, both the staphylococci and the chain-forming micrococci (*Streptococci*) have been regarded as the exciting agents of these pathologic processes.

The pus-producing staphylococci constitute a bacterial group the morphology of which is quite constant, but the members of which differ in certain minor physiologic characteristics, such as pigment-production or the capacity of peptonizing proteid culture media; they also vary as to their pathogenic effects in the human subject or in experimental animals. It will be convenient, however, to consider them under one head, particularly so far as their morbid effects are concerned, since it is a well-determined fact that any one of the races may show extreme virulence or be relatively innocuous. The chief member of this group, and the one most commonly met, is *Staphylococcus pyogenes aureus*, characterized by the golden color of the pigment formed in favorable media and by its virulence. It liquefies gelatin and coagulates milk with resulting acidity. *Staphylococcus pyogenes albus* is closely related to the foregoing, being also a peptonizing organism and coagulating milk, but it is devoid of the power of elaborating pigment like the aureus. Between these two is the lemon-yellow pus staphylococcus (*S. pyogenes citreus*), with its lighter yellow pigment. Then there is a series of nonliquefying staphylococci, represented by *S. cereus albus*, nonpigmented, and *S. cereus flavus*, producing yellow pigment. That several of these cocci, if not all, are but variations of a common stock seems a most reasonable view, although definite scientific proof has not yet been obtained.

These micrococci can exist in saprophytic surroundings, as shown by their presence in water, air, and dust, although as inhabitants of air and dust they have been recovered chiefly from situations like hospital wards, surgical operating-rooms, morgues, etc., where their occurrence may be accounted for readily. They are common in man and the mammals, one nonpigmented variety closely allied to *S. pyogenes albus* being a constant inhabitant of the skin (*S. epidermidis albus*), while other varieties, like *S. pyogenes aureus*, also

abound on the cutaneous surfaces, in the ducts of sweat-glands and sebaceous glands, and about hair-follicles. In the mouth, and more rarely in the nose, auditory canal, or conjunctiva, one or another of these staphylococci is found. As organisms of latent parasitism, the pyogenic staphylococci are also of importance, lying dormant, especially in the superficial lymph-glands, the tonsils, and at times also in the scars of healed infected wounds, in bone lesions, and in the viscera. To this latent microbial parasitism of the lymph-glands, at least, it seems quite reasonable to ascribe some of the peculiar cases of *cryptogenetic infection* in which no demonstrable orifice of invasion is discovered—a form of infection in which the pyogenic micrococci sometimes participate.

Morbid Effects ; Toxic Products ; Immunity.—As their name indicates, the principal races of the staphylococcus group are pre-eminently organisms of suppuration. In the skin their harmful effects are manifested by such lesions as pustular acne, furuncles, and carbuncles ; they are also by far the most frequent agents of inflammation and suppuration in traumatic infective diseases. In inflammation and suppuration of the mucous membranes throughout the body, the pus staphylococci are prominent, either alone or in association with other pathogenic micro-organisms. The same holds true of inflammations of serous membranes. In like manner any of the viscera may be attacked, generally as a secondary invasion from some external local affection. Acute bone affections, such as periostitis and osteomyelitis, are commonly ascribed to these cocci. Multiple synovitis, at first simulating acute articular rheumatism so closely as to be indistinguishable clinically, and followed by acute ulcerative endocarditis and septicemia or pyemia with no apparent local primary affection (“cryptogenetic” staphylococcus infection), is one of the several complicated morbid processes induced by these organisms.

From the preceding rehearsal it is evident that the staphylococcus group may participate both in local and general diseases. From a local lesion like an infected wound, osteomyelitis, or phlegmon, infection may traverse the lymph-channels (lymphangitis) to reach the regional lymph-glands (lymphadenitis), and, while generally stopped by these barriers, it may proceed either by the lymph-vascular or blood-vascular route to more remote parts. Invasion of the systemic blood-stream taking the form of a bacterial septicemia (bacteremia) is a possible consequence, or the cocci may set up suppurative foci in various remote tissues or viscera, producing the condition known as pyemia. In certain parts of the body, particularly from the phlegmons about the nose, retrograde infective thrombosis of adjacent veins may be produced, the thrombi reaching the cranial sinuses and setting up inflammatory or suppurative changes in the meninges, or entering the general venous blood-stream to be taken to the heart, whence the bacteria may be conveyed to the body at large. Again, from the local seat of infection the staphylococci are carried to the heart, here to establish vegetative endocarditis, fragments of the infective vegetations being swept away as emboli to reach certain viscera, where infarction is quickly followed by inflammation and often abscess.

Suppuration as induced by the pyogenic micro-organisms, and particularly by the pyogenic cocci, is a reaction to chemical irritation in which the wandering polynuclear leukocytes take the chief part. Some substance elaborated by the micro-organism and seemingly a part of its protein is of a toxic nature, with the peculiar property of attracting wandering cells when

introduced into animal tissues (positive chemotaxis); these cells, migrating chiefly through the blood-vessels, accumulate in the affected region, accompanied by such vascular phenomena as hyperemia and stasis. A reaction of the fixed-tissue cells is also induced, proliferation resulting. As a further effect of the toxins, the accumulated cellular elements, both migratory and fixed, soon undergo degenerative changes, either albuminous or fatty in nature, and the living and dead cells, cellular detritus, and the liquid substratum make the principal constituents of pus. Sometimes the necrotic phenomena are much more in evidence, gangrene of surrounding tissues with extensive sloughs being caused. In the purulent exudate, the cocci are found both free and inclosed in the protoplasm of the cellular constituents. In many cases this taking-up of the bacteria by the fixed and wandering cells is a protective process (phagocytosis), in which the micro-organisms are inhibited in activity or killed. At other times the polynuclear leukocytes, lymphoid cells, and plasma-cells suffer destruction, and to other cells, especially the large endothelioid phagocytes, falls the labor of removing the detritus. In mild or more chronic suppurative affections and in those undergoing reparative changes, lymphoid cells and plasma-cells—and later mast-cells—make their appearance.

Susceptibility to pyogenic infection is subject to considerable variation, some individuals being easily and repeatedly infected, others enjoying a high grade of active immunity. Many factors, such as previous infections and debility from other diseases, increase the individual predisposition. Many of the influences which arouse latent and apparently healed pyogenic foci into activity are unknown; but cold, traumatism, and incidental diseases are certainly fruitful causes. Of similar nature to the latent foci are the smouldering lesions from which toxic products or attenuated micro-organisms are periodically transported.¹

Experimental inoculation with the staphylococcus group varies considerably in its results. Generally the reaction to subcutaneous injections is a mild and transient inflammation or a localized abscess. Fatal purulent peritonitis is usually caused by sufficiently large intra-abdominal doses, and intravenous injections quite uniformly produce metastatic abscesses in the viscera, and death with general bacterial septicemia. Ulcerative endocarditis may be produced by fragments of potato cultures introduced in the veins or by mechanically injuring the heart-valves before or immediately following intravenous injection of staphylococci, and traumatism or fracture of bones in animals the blood of which contains the cocci is followed by osteomyelitis. Dead pus cocci also excite local leukocytosis and pyogenic reaction.

The peculiar poison upon which the activity of these micro-organisms doubtless depends has not been isolated, but artificial immunity has been induced in animals by injections of the living or dead cocci, and the blood-serum of these subjects appears to have some protective and antitoxic property.

An ordinary external saprophytic coccus, also found as a lodger in the healthy nose, mouth, and throat, which occasionally plays a parasitic and

¹ In this connection, too, it may be well to recall the view lately advanced, that the osseous and nervous lesions (hydrocephalus) of *rachitis* are the result of a chronic infection with attenuated pus cocci or a chronic intoxication with their products; and possibly the lymphoid hyperplasia producing the anatomic picture of the *lymphatic constitution*, as frequently seen in rickets, is a response to the same irritant.

pathogenic role in man, is *Micrococcus tetragenus*, described by Koch and Gaffky, so called because of its prevailing tendency to appear in groups of four elements, comparable to two diplococci side by side. As found in secretions and tissues, it shows a well-defined capsule. It develops readily on ordinary culture media as a nonliquefying, nonchromogenic growth, both in the brood-oven and at room-temperature. Milk is not coagulated, nor are the sugars fermented. Its culture on agar, blood-serum, and potato somewhat resembles that of the pneumobacillus, a resemblance heightened by a "nail" formation in gelatin stabs.

As a pathogenic micro-organism it has been found in localized suppurations, such as abscesses about the teeth, nose, mouth, neck, and axilla, in bronchitis, pleuritis, pericarditis, peritonitis, and even meningitis. Several cases of septicemia ascribed to it have been recorded. It has been noted also in pseudomembranous angina with severe constitutional disturbance. When administered in sufficiently large doses it proves pathogenic for guinea-pigs and rabbits, producing localized abscesses and general hematic infection. White mice are more uniformly susceptible to small doses.

The Pyogenic Streptococci.—The chain cocci of pus are most frequently encountered in their parasitic abode, and while evidently capable of existing, for a time at least, outside of the animal body, such phenomena as their comparatively slow growth on culture media and the short-lived existence of many of the races point to a well-advanced adaptation to parasitism. These characteristics are not uniform, however, and the various pathogenic pus-producing streptococci broadly comprehended under the name *Streptococcus pyogenes* are therefore to be looked upon as a bacterial group of several closely related races or varieties.

Some of the more common variations in form to which these streptococci are subject appear in the length and arrangement of the cocci composing the chains when growing in fluid media, there being cultures in which diplococci alone appear, others with chains of four to six small cocci, and longer chains with both small and larger elements; hence such names as *S. longus*, *brevis*, *conglomeratus*, *gracilis*, and *involutus* have been applied, some observers implying thereby a specific difference, but certainly on insufficient grounds, since it has been found that comparatively slight changes in culture media or a sojourn in the animal organism is effective in changing these morphologic characters. The linear continuity by which the streptococcus chain is produced results from the division of the individual spheres through an axis uniformly at right angles with the chain. But the plane of division is readily disturbed, the consequence being various irregularities in the chain; among other deviations, a division at an acute angle suffices to start a new lateral chain of cocci looking like a branching from the parent series. Various inhibiting or accelerating influences encountered under laboratory conditions further affect the individual cocci, by which is produced the variation in size so often seen; and some similar influence must be concerned in the production of the occasional bizarre streptococcoid elements which assume the shape and general appearance of polymorphous bacilli, like those commonly shown by the organism of diphtheria. By transplantations from blood-serum to broth it was found possible repeatedly to transform the irregular, bacilli-like elements of a certain streptococcus into minute, uniform, split spherules cohering in extremely long chains.

One of the physiologic attributes of this group of micrococci is relatively

constant, viz., the absence of the peptonizing function—they do not liquefy gelatin; but the rate of growth on artificial media differs considerably in streptococci from different sources. Some cloud bouillon uniformly, others aggregate into globules or flakes and settle along the sides or bottom of the tube, leaving the fluid clear; but these differences are unstable, since one and the same stock may be induced to produce both effects in broth. Milk may or may not be coagulated, and some members of the group show a capacity for producing, in artificial cultures, pigment of a yellowish or reddish tinge.

The pathogenic properties of various streptococci, when tested in white mice and white rabbits, are subject to variation not only in different races, but also in the same race according to the mode by which it is handled. By growing nonvirulent or slightly virulent streptococci in certain media, like bouillon-serum mixture, and transferring from mice to rabbits, it has been found possible greatly to accentuate the pathogenic power of a given culture.

Morbid Effects; Toxins; Antitoxin.—Streptococci of the pyogenes group have been found in a diversity of human maladies, often unaccompanied by other bacterial species. As the name of the type species indicates, they are pus-producing, and they may be associated with all the stages of pyogenic infection, from local inflammation to general septicemia. As excitants of local inflammatory and suppurative phenomena, they are encountered in all mucous and serous membranes of the body, in bones, and in abscesses of such organs as the liver and brain. Among the more common affections in which streptococci are concerned, either alone or combined with other organisms, spreading phlegmon and cellulitis, anginas, lobular pneumonia, synovitis and osteomyelitis, lymphangitis, pleuritis and peritonitis, and puerperal septicemia may be mentioned. Besides this, the chain cocci are constantly found in erysipelas, as originally shown by Fehleisen. It was formerly thought that the streptococcus found by Fehleisen in erysipelas was specifically different from those concerned in the other inflammatory suppurative or septicemic conditions, whence arose the distinctions *Streptococcus erysipelatis* and *Streptococcus pyogenes*. However, it has been satisfactorily demonstrated that the streptococcus of erysipelas may become pyogenic, and *vice versa*. The conditions which they induce depend upon the route by which they gain access to the body, and especially upon their virulence, which, as has already been indicated, may be exalted to an extraordinary degree by certain conditions of cultivation and passage through animals. In short, it has been shown that the activity of a streptococcus which only causes abscess may be exalted to a virulence by which erysipelas, purulent infiltration, or fatal septicemia results. These experiments serve to sustain the views as to the common ancestry and close relationship of the various streptococci, as already indicated by morphologic and physiologic considerations, and to emphasize the desirability of considering them as a single group.

Besides their more active manifestations, streptococci may lie latent, as mentioned in connection with staphylococci.

The morbid histology of general streptococcus lesions is quite similar to that seen after infection by the other pyogenic cocci; hyperemia, blood stasis, emigration of leukocytes, and transudation of serum mark the inflammatory reaction. Various local necrotic effects are seen in the virulent infections, although the tendency to transudation and swelling is more marked than the necrotic and liquefying action in local staphylococcus disease. From the absorption of toxins, or in virtue of the diffusion of the cocci, thrombosis,

embolism, infarction, and focal necrosis occur. In erysipelas the organisms generally invade the lymph-channels, spreading rapidly through them, and at times packing them full. Necrotic alterations appear in the surrounding tissue-cells, and wandering cells are attracted, leading to a dense cellular infiltration, in the midst of which the cocci appear, either between the cells or inclosed in those of phagocytic power. The epithelium of the surface may soften and be raised by transuded fluid, producing vesicles. As a rule, the invasion of outlying areas is first effected by the streptococci, which precede the accumulated leukocytes in their march.

The effects of spontaneous streptococcus infection may be reproduced experimentally both by means of the living organisms and by means of the toxins which the streptococci elaborate in fluid cultures. But these poisons have not been isolated, and they are known only by their effects, which are more or less virulent according to the activity of the stock culture, which, as we have already indicated, may be enormously increased by artificial means. Various animals, when subjected to injections of streptococci of increasing virulence or of toxins of increasing strength, attain an immunity manifested by their resistance to large doses of the most virulent cocci or their poisons and by the presence of an antitoxic substance in their blood-serum. Such a streptococcus antitoxin is manufactured and offered as a therapeutic agent for spontaneous streptococcus infections in man, but the practical results have been far from brilliant. The same may be said of the value of streptococcus toxins and antitoxins for the treatment of inoperable malignant tumors.

Micrococcus Lanceolatus and Meningococcus.—The *Micrococcus* or *Diplococcus lanceolatus* must be looked upon as the specific causative agent of genuine lobar or croupous pneumonia; it has been known under various names since 1880–81, when it was discovered in human saliva by Sternberg, and independently by Pasteur.¹ It often appears in short chains of four to six members or even in longer series. Aside from occasional chain formation, there are other characteristics of the lanceolate diplococcus that show it to be a close relative of the *Streptococcus pyogenes*, and those who have worked most extensively on the question of its variation as encountered under natural conditions and laboratory modifications incline to the view that it is only a variety of the *Streptococcus pyogenes* group. If this is true, it must be regarded as a more highly developed variety in parasitic adaptation, since it has not been found under external saprophytic surroundings and is unusually short-lived under the most favorable laboratory conditions. Like other pathogenic micrococci, it is a lodger or inhabitant of the secretions of healthy human beings; but it is more especially confined to the mucous membranes and secretions of the upper air-passages, abounding in the saliva, in the throat, nose, tonsils, or accessory nasal sinuses, although apparently not flourishing on external surfaces like the skin.

Considered as a species, *Micrococcus lanceolatus* owes its morphologic distinction to the triangular or lance-shaped form of the individual elements of the coccus, whence the name “lanceolatus.” A capsule, appearing about the diplococci when present in sputum or in the blood, is also characteristic. But these morphologic features are inconstant and are liable to variation, especially under conditions of artificial cultivation. Physiologically the

¹ Other names are *Pneumococcus*, *Microbe septicémique du salive* (Pasteur), *Micrococcus Pasteuri* (Sternberg), *Pneumoniemikrokokkus* (Fränkel), *Diplococcus pneumoniae* (Weichselbaum), *Streptococcus lanceolatus*, etc.

behavior, as exhibited in its growth on agar, gelatin, potato, in broth, and in milk, is similar to that of the chain coccus of pus, only that it is somewhat more susceptible to change in temperature and is of briefer longevity. Its pathogenic properties, as tested upon rabbits and mice, is more uniform than that of the various races of streptococci, a fatal septicemia being generally produced by relatively small doses injected subcutaneously or intravenously. Injections into the peritoneal cavity produce peritonitis and septicemia; those in the lung or trachea, pneumonia; in the meninges, meningitis; in the joints, synovitis; and small subcutaneous injections cause local abscesses.

Morbid Effects; Immunity.—As shown by Fränkel and substantiated by the exhaustive studies of Weichselbaum in 1886, this coccus is the particular parasite of lobar pneumonia. In all probability this formidable disease must, in certain cases at least, be looked upon as an *auto-infection* by micrococci constantly inhabiting the upper air-passages in health; and while we do not know precisely what conditions conspire to increase the virulence of the micro-organism or to lower the resistance of the host, something of this kind must happen to enable the parasite to pass the barrier afforded by the healthy ciliated epithelium of the upper air-tubes and to overcome the resistance of phagocytic cells. Undoubtedly such local disturbances as angina, tonsillitis, rhinitis, and the like, play a part in opening the way for the further advance of the infection, and at times it seems that the organism of pneumonia has already entered the blood-stream from some local portal of invasion, like the tonsils, before the morbid process in the lungs has made headway. As a result of the irritation of this infection in the lungs, a cellular exudate appears in the pulmonary alveoli, composed at first of cells with single nuclei larger than ordinary leukocytes, mixed with red blood-cells. Polymorphous leukocytes are not present in the earlier stages of lobar pneumonia. Lymphocytes and later plasma-cells make their appearance in the alveoli and the interstitial tissues. Leukocytes with polymorphous nuclei abound in the affected tissues by the third day, and from this period large mononuclear endothelioid phagocytic cells, with inclusions composed principally of red blood-cells, pigment, and polynuclear leukocytes, are to be found. Fibrin is deposited, at first about the periphery of the alveoli. Thrombi appear in the blood-vessels, especially the capillaries, and in the stage of gray hepatization fibrinous thrombosis may attain a widespread extent in the affected tissue. Some of the blood-vessels also contain emboli of giant cells from the bone-marrow, and in certain cases parenchymatous emboli are quite numerous. As resolution advances, plasma-cells become more abundant and mast-cells not infrequently make their appearance. That the epithelium of the pulmonary alveoli suffers damage is evident from the number of exfoliated cells appearing in the pneumonic exudate. The source of the cells first appearing in the exudate is not clear; they probably arise by proliferation from the lining cells of the alveoli. Similar cells appear in the early stages of the pleural exudation which so commonly accompanies lobar pneumonia, and here lymphoid cells, polynuclear leukocytes, large phagocytes, fibrin, and plasma-cells are found as the process advances. Excessive localization of leukocytes and transudation of serum lead to empyema, which not rarely follows lobar pneumonia.

But while lobar pneumonia is the chief affection to be ascribed to the lanceolate micrococcus, it is by no means the only pathologic process in

which this organism participates. Complications of lobar pneumonia, like pleuritis, pericarditis, endocarditis, peritonitis, and meningitis, are also due to its pathogenic effect, either alone or in company with one of the commoner pyogenic cocci. A general blood-invasion, with wide dissemination of the diplococcus (diplococcemia), is also possible, and sometimes the pneumonia seems to be but one of the local expressions of such an infection. On these occasions the general visceral changes peculiar to acute infectious diseases are found, and these parenchymatous changes, affecting principally the lymph-glands, spleen, kidneys, and liver, are present in whole or in part in fatal pneumonia where the inflammatory process remains confined to the lungs. Bronchopneumonia is sometimes produced by this coccus, and it also takes part in such diseases as synovitis, periostitis and osteomyelitis, adenitis, parotitis, mediastinitis, pericarditis, endocarditis, appendicitis, peritonitis, otitis, and meningitis, in which no primary pulmonary affection has occurred. It is very significant that, in many of these diseases, angina, rhinitis, or tonsillitis precedes the more distant affections. Phlegmonous affections and abscesses sometimes contain *M. lanceolatus* in pure culture.

In human beings who have recovered from pneumonia, a protective and curative substance is said to be present in the blood-serum; but satisfactory experimental proof of this statement is lacking, and there certainly is little ground as yet for the use of this serum for therapeutic purposes in man. Immunity in the highly susceptible rabbit may be secured by intravenous injections of small amounts of a potent culture or by the use of filtered cultures or cultures heated to 60° C., but the serum in these cases is of questionable protective value. More recent experiments in rabbits, goats, and horses with cultures of highly developed virulence seem more promising, for the serum of the immunized animals gives experimental evidence of possessing protective and curative virtues; but as for use in actual human therapy, there is little at the present time to indicate the value of such an agent. It has been found, however, that the serum of human beings suffering from pneumococcus infection, or of animals artificially infected, causes agglutination of these micro-organisms.

Apparently even more highly adapted to a parasitic existence than the organism we have just considered is the meningococcus (*Diplococcus intracellularis meningitidis* of Weichselbaum), which is found principally in the substance of polymorphonuclear leukocytes from one or another of the several lesions with which it is associated. Both its biscuit shape and its intracellular abode liken it to the gonococcus. Subjected to the usual conditions of laboratory cultivation, this organism thrives but poorly; it rarely grows on any medium except coagulated blood-serum, and here only scantily, quickly dying in the original culture or when transferred to glycerin-agar or broth. There is nothing characteristic about the cultures except their feeble vitality, and nothing is known about variations in morphology or physiology. Contrary to the rule for the pyogenic staphylococci, streptococci, and Micrococcus lanceolatus, the meningococcus does not retain the stain when treated after the Gram or Weigert method.

The diplococcus intracellularis is considered by many observers the specific etiologic agent of epidemic cerebrospinal meningitis. Certainly the majority of cases of acute meningitis, endemic or epidemic, have either the lanceolate micrococcus or the meningococcus associated with them, and it seems proper to charge this affection chiefly to them. Both organisms have their abode in

the nose; through the ready route afforded by the accessory nasal sinuses, infection of the meninges is easily produced, especially when the resistance of the mucous linings of the nose and sinuses is lowered by catarrhal affections. It is not impossible that in this way the diplococci or some other pyogenic cocci gain access to the meninges, brain, and spinal cord, exciting not only the acute purulent form of meningitis, but also the more chronic forms, like meningo-encephalitis, the consequences of which are seen in infantile paralysis, idiocy, etc.

Besides being found in acute meningitis, the meningococcus has been discovered also in the pneumonic lung, in synovitis, in abscess of the myocardium, in multiple arthritis complicating meningitis, and in tonsillar abscess and pseudomembranous conjunctivitis associated with meningitis. It has been demonstrated in the circulating blood during life, thus showing that it may cause a condition of general septicemia; and a valuable diagnostic procedure is its discovery within the polynuclear leukocytes of the meningeal fluid obtained by lumbar puncture. Not uncommonly it is mixed with other pathogenic organisms, especially the pathogenic cocci. In experimental animals, subcutaneous inoculations of pure cultures of the meningococcus are not fatal; but, when introduced into the peritoneum or pleural cavity, fibrinopurulent inflammation results, usually ending fatally. Cerebrospinal meningitis has been produced in the goat by subdural inoculation of a broth suspension of the organism.

Histologically the meningitis provoked by this organism resembles ordinary suppurative leptomeningitis. The meningeal exudate consists principally of polynuclear leukocytes, of large endothelioid cells, and some fibrin. Lymphocytes appear in the perivascular sheaths of the blood-vessels.

Gonococcus.—The biscuit-shaped diplococcus discovered by Neisser in 1879, and styled *Micrococcus* (*Diplococcus*) *gonorrhæa*, or simply gonococcus, is the specific etiologic factor in gonorrhea. Morphologically it most closely resembles the meningococcus, agreeing also in its refusal to retain the stain after the procedure of Gram. Nothing is known of its capacity to exist under saprophytic surroundings, all evidences pointing to its advanced adaptation not only to a state bordering on obligate parasitism, but also one apparently necessitating the choice of the human body as a habitat, for it has never been found as a parasite in other animals. For a long time, failure attended all efforts to cultivate it artificially; but with improved media, especially those containing proteids from the human subject, as obtained by mixing ascitic or hydrocele fluid or human blood-serum with agar, cultures have been obtained. The further addition of human urine appears to improve the serum-agar. On these special culture soils a growth of the gonococcus is obtained by smearing the secretions, such as urethral pus, over the surface and placing the cultures in the thermostat. For ordinary clinical demonstration, however, the discovery of the characteristic biscuit-shaped diplococci or tetrads in the suspected secretion, particularly when lying in heaps in the protoplasm of polynuclear leukocytes, and their failure to stain by Gram's method, generally suffice for diagnostic purposes.

Morbid Effects.—Contrary to the ideas originally held, the gonococcus is not confined to the urethral lesions and discharges of gonorrhea. This fact has been strikingly brought out since the introduction of successful culture methods, and we now know that it is associated with a variety of local conditions that may complicate gonorrhea. In ophthalmia neonatorum its

presence has also long been known. But it has remained for comparatively recent investigations to establish its association with arthritis, tendosynovitis and perichondritis, salpingitis and localized peritonitis, acute and chronic cystitis and pyonephrosis, adenitis, pleuritis, myocarditis, and ulcerative endocarditis. That the gonococcus may even produce a general blood-infection seems proved. There is no doubt concerning the pronounced pyogenic activity of this coccus. It produces both local inflammatory and suppurative reactions in the mucous membrane of the genito-urinary tract and of the eyes, and induces the various metastatic purulent or seropurulent processes which have been enumerated.

Experimental inoculations have not yielded brilliant results, doubtless on account of the unsuitability of the lower animals as hosts; but local inflammation and suppuration follow the introduction of living gonococci on sterile foreign substances, and dead cultures provoke a nonpurulent peritonitis. Typical gonorrhea has been produced in man by inoculations of pure gonococcus cultures into the urethra, but the mucous membranes of animals seem entirely refractory to inoculations both with cultures and with gonorrheal pus. The toxic substances to which the gonococcus owes its pathogenic activity are not well known. They appear to reside in the bacterial cell, since the dead organisms are capable of causing the usual inflammatory reaction. It has been found possible to render experimental animals refractory to gonococcus inoculation by the use of graduated doses of the living or dead organisms, but no success has thus far attended the efforts to obtain a preventive, protective, or curative serum from gonococcus-immune animals.

PATHOGENIC BUDDING AND FILAMENTOUS FUNGI.¹

Introduction.—Long before the bacteria were considered as pathogenic agents, certain organisms belonging to the higher Thallophyta (algæ and fungi) of the great subdivision of Cryptogamia (flowerless plants) were recognized as factors in human diseases. In 1837 the parasite of favus was seen by Remak; again noted by Schönlein in 1839; and, together with the fungi concerned in thrush and herpes tonsurans, accurately described by Gruber in 1841–1844. Since these early descriptions a large number of thallophytes have been found upon or within the human body, sometimes existing as messmates or passenger parasites, again as harmful, disease-provoking invaders. Within the last few years new species have been discovered, some of them concerned in grave morbid processes, so that the study of the pathogenic nonbacterial fungi has become an important branch of pathology (pathologic mycology). Not all the fungi belonging to the nonbacterial Thallophyta are parasitic, of course; a considerable number of

¹In the discussion of this topic, free use has been made of Blanchard's section, "Parasites Végétaux et l'Exclusion des Bactéries," in the *Traité de Pathologie Générale* of Bouchard, tome ii., and his classification of these pathogenic organisms has been adopted in most part. For a more exhaustive treatise, the student is referred to this article. Good reviews with bibliographies will be found in Eppinger's *Die durch Cladothrichsen (Streptothrichsen, etc.) hervorgerufenen Erkrankungen*, and Ricker's *Spross- und Schimmelpilze beim Menschen*, in *Ergebnisse der allgemeinen Pathologie und pathologischen Anatomie des Menschen und der Tiere* of Lubarsch and Ostertag, Erste Abteilung, and in Busse's *Ueber pathogenen Hefen und Schimmelpilze*, *ibid.*, Fünfter Jahrgang, 1898. A detailed consideration of pathogenic yeast fungi is presented in Busse's monograph, *Die Hefen als Krankheitserreger*, Berlin, 1897. An older but still valuable work is Baillon's *Traité de botanique médicale cryptogamique*, Paris, 1889. The current journals on Parasitology and Pathology should also be consulted.

groups, such as the algæ, slime-moulds, seaweeds, contain chlorophyl and are independent aquatic plants (marine or fresh-water), while many others pass an exclusively saprophytic existence. But it is particularly among chlorophyllless thallophytes that a large group of parasitic vegetable organisms is found, many infesting various kinds of higher plants, low and high orders of animals, and finally man. Among the fungi parasitic upon plants, one has but to recall the blights, rusts, smuts, moulds, and mildews, which sometimes do great damage to fruits and vegetables. They also infest lower animals, notably insects, which often succumb to their ravages, a familiar example being the fly fungus (*Entomophthora museæ*).

In botanic position the fungal thallophytes stand lowest in the scale of cryptogams, coming in relation with the asexual, unicellular schizomycetes. This contact with the bacteria is so close as to render distinction a matter of difficulty, especially in the case of the more minute fungi, and our knowledge is still too indefinite to make distinctions final. The same considerations apply to the matter of classification of these fungi, which has already undergone several revisions and is still far from perfect. As a rule, however, these organisms are larger and therefore more readily studied than bacteria, and many of them exhibit characteristic sexual processes. But as in the bacteria, the morphologic variation to which these fungi are subject often becomes confusing, and it is through the different interpretations placed upon these variations that disagreement among systematic mycologists has arisen. As a case in point, it may be remarked that some authorities deny the existence of yeast fungi (blastomycetes or budding fungi) as an independent order, claiming that the usual oval yeast-cells are only conidia or nonsexual spores of filamentous fungi.

The *morphology* of the higher parasitic fungi is more complex than that of bacteria. The characteristic structure of the organisms is the vegetative body or thallus, generally a mass of filaments or threads, termed *mycelium*, the single threads of which are *hyphæ*. The thallus takes the place of the root, stem, branches, leaves, and flowers of the Phanerogamia, and, instead of producing seeds to further the reproduction of the fungi, round or oval bodies called *spores* are formed. The spores multiply by a process of budding or gemmation, which in certain species, like the yeasts, becomes widely diffused. Under proper vegetative conditions the spore gives rise, by a process of germination, to a mycelial filament which ramifies more or less extensively, and generally remains unicellular in spite of the considerable size it sometimes attains. The continuity of the mycelial hyphæ is not broken by a regular process of division, but by the formation of walls or *septa* at irregular intervals. The vegetative stage terminates by the formation of organs of fructification which produce the spores, these organs appearing on special hyphæ distinguished from the remainder of the mycelium by the limitation of their growth and their special structure. The formation of the spores upon these hyphæ takes various types, of which five may be distinguished, thus :

The *Exospores* or *conidia* (nonsexual spores) arise on the extremity of the germinal hyphæ by a process of budding or septation. The resulting spores are usually arranged in a linear series. In some cases a difference is manifested in the spores: larger ones, *macroconidia*, and smaller ones, *microconidia*, being carried by the germinal hyphæ or *sporophores*, which may be similar or dissimilar. At their formation the conidia are unicellular, but

they may divide and become bicellular or multicellular. They are enveloped by a thick, dense wall and contain nutritive substances, especially of a fatty nature. In this state they can survive a long time.

Endospores or *gonidia* form in the interior of special spore-cases or sporangia, but not by a process of septation of the germinal hyphæ. When free and provided with organs of locomotion (flagella or cilia), they are known as *zoospores*, the spore-case giving origin to them being a *zoosporangium*. *Asci* are a particular form of sporangia, their spores being *ascospores*. The sporangium is frequently terminal and aerial.

Zygosporos are products of a modified sexual act or a conjugation between two special hyphæ, either in the air or within some nutritive medium. These hyphæ send out small special branches, which come in contact, elongate, and take on club-shaped ends, by which they unite. A transverse partition forms at a little distance from each end of the united clubs, the original walls between them disappearing. The new cell now secretes a thick double wall, becomes charged with nutritive material, sometimes with pigment, and this resisting mass or seed is the *zygosporos*. The special branches or *gametes*, the union of which produces the *zygosporos*, are apparently similar, and it is impossible to discover a sexual differentiation.

Chlamydospores are asexual hibernating or resting spores with very thick walls, produced by an enlargement of special cells or branches. The membrane is pigmented and is charged with fat and glycogen.

Finally there are the *Oospores*, thick-walled resting spores borne by terminal or intermediate cells, resulting from a perfect sexual act or fertilization, and therefore strictly comparable with a fertilized ovum. The female element or *oosporangium* (*oogonium*) is provided with a thick wall pierced by pores, and contains one or more rounded masses of protoplasm (germ-cells, female gametes, or *macrogametes*). Fertilization is accomplished by the male gamete or *antheridium*, which forms on a thin special hypha and comes in direct contact with the oogonium, projecting a protoplasmic process into its interior, which fuses with it. In other cases the protoplasm of the antheridium separates into motile bodies (male gamete, *microgamete*, antherozoid, or spermatozoid), which approach the oogonium and fecundate it. In some fungal species, however, fertilization of the oogonium does not precede development, the transformation into an oospore being a process of parthenogenesis.

In a general way, the *life phenomena* of these higher pathogenic fungi resemble those of the bacteria, most of them being saprophytes in the free-living state, and depending on dead animal or vegetable matter for their nourishment. Parasitism in many cases seems an accidental acquisition, especially when the human host is chosen; but certain of these organisms have become well adapted to the parasitic mode of existence, and a few of the thread fungi have reached or approach closely the stage of obligate parasitism. But little is known of the mode by which these thallophytes produce the morbid processes with which they are associated, since they have not been so carefully studied as the bacteria; but, from the similarity of the lesions excited by their presence, it appears that some of them elaborate harmful toxic products, just as bacteria do. In other cases the lesions suggest that a mechanic effect, as by a foreign body, is the chief source of irritation to the invaded tissues.

In considering the individual parasites, two principal divisions of the

Thallophyta claim attention, viz., (1) the *Phycomycetes*, and (2) the *Mycomycetes*, to which must be added (3) unclassified pathogenic fungi.

Pathogenic Phycomycetes.—The phycomycetes are fungi resembling algæ, but destitute of chlorophyl. During active vegetation the mycelium is one-celled, remaining so in some cases, though generally becoming irregularly septate. Many species are aquatic. Reproduction takes place by sexual spores and by conidia or sporangia. Swarm spores (zoospores) occur in some species.

Phycomycetes are divided into three groups, with many families: *Chytridiæ*, or the zoosporous group; the *Oomycetes* or Oosporaceæ; and the *Zygomycetes* or Zygosporaceæ. No chytridiaceous fungi are known as human parasites.

The *Oomycetes* are divided into two principal families: the aerial *Peronosporaceæ*, comprising the mildews and white rusts, which are parasitic on the Phanerogamia, especially the Dicotyledons, and illustrated by the potato mildew, *Phytophthora* (*Peronospora*) *infestans*, or the mildew of the grape, *Peronospora viticola*; and the aquatic family *Saprolegniaceæ*, with three genera, *Achyla*, *Saprolegnia*, and *Leptomit*us. Representatives of the first two genera are to be found in the dead bodies of insects falling in the water. *Leptomit*us *lacteus* is found on submerged organic débris and in water-supply pipes, where it has been suspected of tainting the water.

Several species of *Leptomit*us have been described by mycologists as occurring in the human body, some of which are placed in this category on meager grounds. Thus, *Leptomit*us *urophilus*, found in urine; *Leptomit*us *Hanoveri*, from the coating of esophageal excoriations; *Leptomit*us *utericola*, from granulations in the cervix uteri; *Leptomit*us *uteri*, from a uterine flux resembling pus; and *Leptomit*us *oculi*, from the aqueous humor obtained by corneal puncture of an eye afflicted with rheumatic iritis. Some of these fungi probably followed accidental contaminations of the fluids in which they appeared, and it is questionable whether *L. Hanoveri*, *L. utericola*, and *L. oculi* belong to the genus *Leptomit*us. A more common representative of this genus, presenting at least two varieties, is *Leptomit*us *vaginae*, which appears to provoke a mild chronic vaginitis, with itching and a discharge. In view of the recent discoveries of filamentous fungi (classed as *Sporothrix*) in refractory subcutaneous abscesses of the hand and arm, it is interesting to note the so-called *Leptomit*us *epidermidis* (of Küchenmeister), discovered and described by Gubler, which form long, branching filaments, accompanied by ellipsoidal spores, isolated or in groups of two. This fungus was found in small white pustules which developed on the back of the hand and fingers of a young man, who had been shot through the hand, which was treated by continuous irrigation.

Among the *Zygomycetes*, several organisms of importance to the pathologic mycologist are found. The group is characterized by the production of resting spores (zygospores) from a process of conjugation in which two similar club-shaped hyphæ participate. Nonsexual spores or conidia, endospores or gonidia, and chlamydospores are also formed. One of the two principal zygomycetous families, *Entomophthoraceæ*, is parasitic in insects of various kinds, a familiar example being *Entomophthora museæ*, the fly fungus, which is so destructive to the house-fly in the autumn.

The *Mucoraceæ* (or Mucors) constitute the other family of zygomycetes of interest to us, and they are typically represented by *Mucor mucedo*, com-

monly appearing on moist bread. They are widely distributed in nature, being chiefly saprophytic; a few only are parasitic. There are three principal genera: *Mucor*, *Rhizopus*, and *Monterella*; and Blanchard also includes the genus *Cercosphaera*.

Under ordinary conditions, certain species of mucors are nonpathogenic in man (*M. mucedo*, *Rhizopus stolonifer*). Others thrive at the body-temperature and provoke morbid conditions. Among these species are *M. pusillus*, *M. corymbifer*, *M. septatus*, *M. ramosus*, *Rhizopus racemosus*, and *R. rhizopodiformis*. In the first instance these fungi, which find their way into the body-cavities through the medium of air, water, and food, comport themselves as mildly harmful messmates. For example, *M. corymbifer* has been found on the arch of the palate, and a representative of the black moulds (*M. niger*) has been recognized as the cause of a chronic dark coating of the papillæ on the back of the tongue. The external auditory canal and the exposed face of the tympanum also furnish the habitat of certain species of mucor, as well as of *Aspergillus* (otomycosis). At other times the mucors participate in a more extensive local internal process, as in the case of pulmonary mycosis described by Cohnheim and Fürbinger (pneumomycosis). Finally there are cases of generalized mucor infection in which the spores are carried by the blood-stream, lodging in various parts of the body and forming mycelial filaments with the production of serious lesions. Such a case has been described by Paltauf, who made an autopsy in a case of death by coma after symptoms of enteritis and peritonitis, and found intestinal ulceration and hemorrhagic foci, focal pneumonia, cerebral abscess, suppurative laryngitis and pharyngitis, and splenic tumor, with the presence of a mucor (probably *M. corymbifer*) in the various lesions. *M. ramosus* has been found in the auditory canal, producing a very persistent brownish false membrane, causing earache and buzzing. Experimental general fatal mycosis has also been produced by the intravascular injection of spores of *M. corymbifer*, *R. rhizopodiformis*, *M. pusillus*, and *R. racemosus* into rabbits, with pronounced renal and intestinal lesions and less frequent involvement of the spleen and bone-marrow.

Cercosphaera Addisoni (Blanchard), variously described as *Microsporon Audonini*, *Torula vulgaris*, *Saccharomyces ovalis*, *Microsporon vulgare*, etc., is a curious fungus generally appearing as oval elements with drawn-out ends (gourd shape), about the size of an ordinary yeast-cell, and not forming a mycelium or chain of spores. During the reproductive phase the nucleus divides, probably by a process of karyokinesis, and by the successive divisions a considerable number of daughter-cells appear in the enlarged mother-cell. When placed in suitable fluid media, these daughter-cells become motile, flagellated zygospores. It is highly probable that these flagellate embryonic forms are the agents which penetrate the horny layer of the epidermis, from which arises the peculiar form of red or bronze pityriasis with which the parasite is associated. It was the bronzed hue of the infected skin that led to the confusion of this parasitic cutaneous affection with Addison's disease. This mycotic pityriasis is contagious.

Pathogenic Mycomycetes.—The mycomycetes are higher fungi, generally aerial, and having from the start a many-celled mycelium which increases in length by additions to the terminal cell, and are thus distinguished from the phycomycetes, which have a one-celled thallus that becomes septate only at the period of sporulation. Some of these fungi present a

comparatively simple organization; others become quite complex, some of the simpler forms doubtless representing underdeveloped examples of higher forms. They are divisible into four great groups: the *Uridineæ* or rusts, and the *Ustilagineæ* or smuts, which are parasitic on higher plants; the *Ascomycetes* and the *Basidiomycetes*, including the puff-balls and toadstools. We shall consider particularly the ascomycetes or sac fungi, which are characterized by the production of asci or ascospores, a mode of fructification equivalent to the formation of endospores in the sporangium. Fructification by conidia-like sprouts also occurs, taking a variety of forms. The ascomycetous fungi are separated into four orders: the Gymnoasceæ (including the Blastomycetes), the Perisporaceæ, the Spheriaceæ, and the Discomycetes. From the standpoint of pathologic mycology our interest naturally centers in the blastomycetes or yeasts, which occupy an important position among the pathogenic human parasites. As the type of this class of fungi, the familiar yeast of beer (*Saccharomyces cerevisiæ*) may be taken, and its morphologic and physiologic peculiarities will illustrate the biologic phenomena of blastomycetes in general. These organisms are round or oval cells with a cell wall of single or double contour and a protoplasmic internal mass, often containing granules and frequently exhibiting vacuoles. They are characterized by their method of propagation, by budding during active vegetative existence—whence the name, budding fungi, applied to the order. Under unfavorable nutritive conditions or in the absence of oxygen, they multiply by the formation of endospores or *ascospores*. While generally unicellular plants, the yeasts are not invariably so, since the cells can elongate to form mycelial hyphæ; and at times a complicated ramifying septate mycelium is produced, especially when these organisms are grown in certain culture fluids, such as fluid beer-wort. At this time side buds, which separate into conidia-like bodies, may also appear on the hyphæ. While the property of fermenting fluids containing sugar is common among the saprophytic yeasts, it is not a universal function, being often absent among the parasitic forms.

Our knowledge as to the biology of the budding fungi is still meager, and for this reason a classification of the pathogenic species cannot be attempted. Indeed, it is quite probable that with further information some of the fungi now included in this order will be otherwise placed. For the present purpose, therefore, we shall content ourselves with briefly reviewing the blastomycetes described as pathogenic, retaining the nomenclature as at present applied. It is generally the custom to divide the blastomycetes into certain genera, *e. g.*, *Saccharomyces*, *Oidium*, *Monilla*, etc.

One species, classed with *Saccharomyces cerevisiæ* on insufficient grounds, has been found in the coating on the human tongue, in vomited matter, in diarrheal stools, in the vagina, and in diabetic urine. Neumayer believes that under certain conditions these organisms, which from their widespread occurrence easily find their way into the human alimentary canal, can produce diarrhea and flatulence. Other species of *Saccharomyces* have been found in the purulent discharge of otitis media. Calmette observed yeasts in the blood, sputum, and urine of a case of typhus. An undetermined species of *saccharomyces* was also found by Troisier and Achalme in a pseudomembranous angina occurring in a patient suffering from typhoid fever, and this observation has recently been confirmed in other quarters. *Saccharomyces ruber* (Demme) of red raspberries has been held responsible

for the production of a family outbreak of intestinal catarrh, having contaminated the milk drunk by several of the children.

The most important communication on the subject of human saccharomycosis, and the one which has served to stimulate the present active study of this branch of mycology, is that by Busse, who in 1895 obtained pathogenic blastomycetes from a woman suffering with a peculiar cystic swelling of the tibia, which on histologic examination showed a sarcomatous-like structure of young granulation-tissue and giant cells. From the viscid fluid evacuated from the original tumor, and from the tumor-tissue, yeast-like fungi were obtained and isolated in culture. Thirteen months after the appearance of the tibial neoplasm the patient died, and at autopsy diseased foci, some reaching the size of an apple, were found in the lungs, kidneys, and spleen, in which the yeast organism abounded, lying singly or in colonies. A vesicle on the cornea also contained the fungi. The visceral lesions resembled those of a chronic inflammatory process with caseous and fatty degeneration, and contained an abundance of the parasites. Pure cultures of this yeast fungus were pathogenic for certain animals, particularly mice and rats, in which a chronic granulomatous neoplasm appeared about the injection-site, together with miliary granulation-tissue nodules in the lungs, kidneys, and brain. This organism grew well at room and incubator temperature on ordinary media, producing white, noncharacteristic cultures which did not liquefy gelatin. On special media to which malt extract was added, the growth was more profuse; and on prune-decoction and potato, grayish or even black cultures were produced. Acid media were especially suitable. Media containing glucose were fermented with the production of alcohol and carbon dioxid. Multiplication of this species occurred in the form of gemmation or budding exclusively, the production of endospores not having been observed.

Another blastomyces closely resembling that just mentioned is *Saccharomyces subcutaneus tumefaciens*, described by Curtis in 1896, and obtained by him from myxomatous neoplasms appearing beneath the skin of the thigh and in the neck of a young man, and also in a large purulent ulcer in the loin. The nodules were composed of a myxomatous tissue, richly cellular and resembling sarcoma. The yeasts were numerous both between the cells of the neoplasm and within them (blastomycetic cell inclusions). They were very easily cultivated, and produced ethyl alcohol and acetic acid in saccharose solutions. Rats, mice, dogs, and rabbits were susceptible to inoculations with cultures of this organism, a chronic infection with the production of multiple foci of subcutaneous inflammation and proliferation being provoked. Endosporous division was regularly observed in old cultures of this species. Corselli and Frisco also record a case of saccharomycosis in which tumor-like nodules (described by the authors as sarcoma) were found in the omentum and mesentery, and in which the yeast fungi were discovered in the chylous ascitic fluid obtained by exploratory puncture during life. The organisms were cultivated and found to be pathogenic for guinea-pigs, rabbits, and dogs.

From the morphologic resemblance of the blastomycetic nodules to tumors, and the fancied resemblance of the yeasts lying in animal cells to the cell inclusions appearing especially in malignant tumors, the blastomycetic theory of the etiology of tumors was promulgated in Italy by Sanfelice, Roncali, and others. That these investigators occasionally recovered yeast

fungi from true tumors seems undoubted, but their conclusions as to the etiologic relations of these organisms are apparently premature, since none of the species reproduced tumors entirely typical of those spontaneously arising in man; and of the various pathogenic blastomycetic species obtained from morbid processes in man or under saprophytic conditions, all failed to produce anything else than "pseudotumors"; that is, nodules of a chronic inflammatory character, containing enormous numbers of the yeast organisms in a granulomatous matrix. A careful experimental study of a series of wild yeasts was made by Rabinowitsch, who found several pathogenic species, some of which produced a septicemia, while others gave rise to granulomatous nodules.

Since the description of the first case by Gilchrist in 1894, we have learned that yeast fungi are also concerned in skin-affections (cutaneous blastomycoses) taking the form of a dermatitis (blastomycetic dermatitis), as

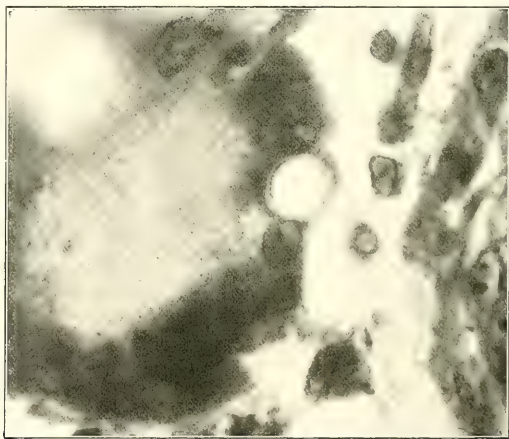


FIG. 97.—Blastomycetic dermatitis, showing a vacuolated blastomycetes in the border of a giant cell. $\times 1200$. (Author's case; from a photomicrograph.)

noted in the cases of Gilchrist, Gilchrist and Stokes, Wells, Hektoen, and others. In Busse's case above noted, the skin in several regions became involved in an ulcerative process, from which the yeast fungi were obtained. The affection described by these writers takes the form of a chronic diffuse inflammatory affection resembling scrofuloderma or even lupus vulgaris. There is a marked epithelial hyperplasia, associated with the formation of giant cells and of miliary abscesses in the epithelium and subcutaneous tissue. Necrosis and ulcerative defects appear, and inflammatory granulation-tissue or scar-tissue may be formed to make good the defects. There seems to be considerable difference in the organisms thus far described in connection with these cases, and it is probable that at least two distinct species of the yeast fungus are concerned. Indeed, it is not impossible that one or more of these organisms, which produce well-marked mycelia, lateral buds, conidia, and pigment, may be found to belong elsewhere among the

fungi. Those which have been studied agree, however, in producing nodules of a chronic inflammatory character when injected into various animals, like the dog, horse, sheep, guinea-pig, rabbit, rat, and mouse. The inoculated animals generally pass into a state of marasmus, probably due to a slow toxemia, while the parasites which localize in favorable organs and tissues set up chemotactic and necrotic changes, followed by a process of granulation resulting in tubercle-like nodules. That suppuration may be produced by pathogenic blastomycetes has been determined experimentally.

Saccharomycosis of the mucous membranes is also possible, pathogenic yeast fungi having been obtained from cases of chronic catarrh of the uterine cervix by Colpe and Buschke, and from proliferative catarrh of the nasal mucosa by Busse. Saccharomycetes have also been found in the secretion from a case of peculiar inflammation of the conjunctiva and cornea.

Several diseases among the lower mammals are also ascribed to a blastomycetic origin, as, for instance, a farcy-like affection of horses (*lymphangitis epizootica*), characterized by a chronic inflammation of the lymphatics and lymph-glands, in which proliferation and nodular thickening are produced, later followed by a purulent softening. The parasite is probably identical with *Cryptococcus farciminosus* of Rivolta; it is smaller than *Saccharomyces cerevisiæ*, and does not ferment sugars. And in guinea-pigs a pulmonary affection closely resembling tuberculous pneumonia is spontaneously produced by a species of saccharomyces (*Saccharomyces niger*, Maffucci and Sirleo), and the same species has been obtained from a spontaneous intestinal affection of guinea-pigs, localized especially about the cecum, in which thickening and ulceration of the mucosa were produced, with enlargement of the mesenteric lymph-glands and small nodules in the peritoneum. Epithelioma contagiosum of fowls and the so-called pox of doves are believed to be blastomycoses.

In the genus *Oidium*, tentatively included in blastomycetes, only one representative—long since recognized as associated with thrush—need concern us now, viz., *Oidium albicans* (Robin), also variously described as *Saccharomyces albicans*, *Monilia albicans*, etc. This disease is localized in the mucosa of the mouth, throat, esophagus, or more rarely in the epiglottis, trachea, bronchi, stomach, vagina, or nipples of nursing women. It is especially frequent in the mouths of infants, notably those in a marantic condition, and appears as a white or grayish membranous coating. Acidity of the secretions seems to be necessary to the progress of the disease, and the fungus *Oidium albicans* is very susceptible to alkalies. The organism appears both as spheric or oval budding cells and as tubular septate filaments, these filaments or hyphæ often ramifying to form a mycelium, from the elements of which buds continue to form. In certain media, as the liquid of Nägeli rendered saccharine, *Oidium albicans* produces endospores or ascospores, the minute spores being contained in a large thick-walled terminal cell (chlamydospore), also charged with glycogen. It is probably in this resisting stage that the organism survives and finds its way through the air or other medium to the oral mucosa of human beings. The organism penetrates the mucous epithelium, causing a swelling and desquamation of the epithelial cells; hyphæ also invade the underlying connective tissue, which responds to the irritation with a chronic small-celled proliferation. From these local foci the organisms may occasionally penetrate the blood-vessels, and thus be transported. Schmorl found miliary

abscesses and nodules in the kidneys of a child suffering from typhoid fever and oral thrush, and from these renal lesions and in the spleen he secured the oidium. In a brain-abscess following esophageal thrush in an infant, Zenker found the same organism. A systematic examination of the viscera of thirty-two individuals afflicted with thrush, made by Heller, resulted in the discovery of the fungus within the blood-vessels twelve times, and in thrombi six times. Experimentally it has been found that *Oidium albicans* causes a general mycosis similar to that produced by the pathogenic moulds.

Oidium subtile is the term applied by Blanchard to a fungus found by de Boyer and d'Antin (1881) in a pustular cutaneous affection of a cachectic infant, and it is regarded as identical with one described by Babes (1882) in an ulcerative dermatitis appearing on the abdomen and legs of a woman. The fungus resembled *O. albicans* somewhat, though its filaments were more slender. Terminal conidia arranged in linear series are formed; and while the mycelium branches at right angles, these branches are less numerous than in *O. albicans*. It is possible that some of the so-called yeasts of blastomycetic dermatitis belong in this category, and this is strongly urged by Giuseppe Cao.

Another species somewhat resembling the foregoing, but whose affinities have not been accurately determined, is *Rhodomycetes Kochi*, found by von Wettstein (1885) in the stomach in certain cases of pyrosis, where it formed a sporogenous fungous layer on the gastric mucosa.

The second ascomycetous order claiming attention is **Perisporiaceæ**,¹ which includes the fungi characterized by the formation of a mass of ascospores of varying numbers, arranged side by side to form a compact mass called the *perithecium*. Ordinarily this perithecial mode of fructification is not seen, the fungi developing asexually from a kind of conidial sporulation which is subject to various modifications. The order has been divided into *Erysipheæ*, represented by the blights to be found on various phanerogamia; *Tuberaceæ*, represented by the truffles; and *Aspergilleæ*, including a number of common moulds. *Aspergilleæ*, which concern us particularly, are represented by three genera, the first of which is *Penicillium*, which is typified by the blue-green bread-mould, and is characterized by a septate conidial hypha terminating in several short branches which swell into flask-shaped ends and give rise to a series of prickle-like extensions, *sterigmas* or conidia-bearers, each of which produces a linear series or chain of spores or conidia at its extremity, the whole fruit-bearing hypha with its sterigmas and conidia resembling a hair-pencil, hence the name of the genus.

The ordinary *Penicillium glaucum*, or bread-mould, has been encountered on the tympanum of the human ear, and in the dog it was found in a case of aural catarrh. Intravenous injections of suspensions of this mould produce a general fatal mycosis in rabbits, with the development of miliary, tubercle-like nodules in the viscera, together with mycotic emboli in the smaller blood-vessels.

A division of aspergillus, hardly of sufficient distinction to be classified as a separate genus, is *Euotium*, characterized by the yellowish hue of its perithecia, which are delicate and easily distinguishable from the hard, woody sclerotium of aspergillus. Representatives of both this genus and subgenus

¹ It was formerly customary to include both Perisporiaceæ and Spheriaceæ under one order, *Pyrenomycetes*.

have been found to possess pathogenic properties either in spontaneous diseases in man or other animals or when used experimentally, the generic names *Aspergillus* or *Eurotium* being often used synonymously, as *A. flavus* (*E. flavum*); *A. fumigatus*; *A. subfuscus*; *E. glaucum* (*A. glaucus*); *E. repens*; *E. malignum*.

Sterigmatocystis resembles *aspergillus*, the species having been confounded at times. It is distinguished by the presence of basidia inserted on the flask-shaped end of the fruit-hypha, to which the sterigmas with their conidial ends are attached. Those of its species which are of pathologic moment are especially *S. antacustica* and *S. nidulans*. It is hardly necessary to say that inaccuracies still exist in the classification of *Aspergilleæ*, some of which have been but imperfectly studied by those able to determine their exact botanic position.

Aspergillar mycosis (aspergillosis) in man is not extremely rare. In a semisaprophytic existence (as commensal or lodger parasites) several species have been found in the external auditory canal, the tympanum, mouth, nose, maxillary sinus, throat, respiratory passages, eyes, genitalia. In several of these situations no apparent harm is done by the fungus. Thus aspergillar otomycosis is not an uncommon affection in apparently healthy persons with no appreciable aural symptoms; but at other times there is a serious purulent, fetid otorrhea, with more or less damage to the auditory mechanism. In such instances the mould fungi are usually associated with pyogenic bacteria, and are scarcely to be held alone responsible for the disease. Among the species encountered in the ear are *A. flavus* and *fumigatus*, *Sterigmatocystis antacustica*, *S. nidulans*, *Eurotium repens*, and *E. malignum*. Several cases of severe infection of the ocular mucosa with corneal ulcer and hypopyon are charged to the *aspergillus* group of fungi; in one such case described by Fuchs, the organism (*A. fumigatus*) also produced corneal ulcer when transplanted to the eye of a rabbit. Fungi of this group have also been found in a few instances of cutaneous disease, especially in a form of ulcerative dermatitis and in a peculiar kind of onychosis (onychomycosis), in which the epithelium of the nail-matrix exfoliates and prepares the soil for the *aspergillus*.

In the respiratory passages of man and other mammals, aspergillar mycosis assumes various types. The fungi sometimes are found developing on the mucosa of the trachea, bronchi, or even in the pulmonary alveoli without noticeable damage, apparently being only harmless lodgers. At other times pseudomembranous affections or necrotic changes and ulcerations of the respiratory tubes are found. But a still more extensive and serious affection is produced by these parasites, which was first recognized in pigeons, but afterward encountered in various mammals and in man. This is a form of pulmonary mycosis taking a tuberculous-like character (*pseudo-tuberculosis aspergillina*). In pigeons the disease attacks the mouth, lungs, liver, or kidneys, appearing either as a pseudodiphtheric affection of the mouth and air-passages or as a tuberculous affection of the lungs, with mycotic nodules in the liver and kidneys. Through the earlier studies of Potain, Dieulafoy, Chantemesse, and Widal, and the subsequent observations of Renon, Gaucher, and Sergent, the interesting facts relative to the pulmonary mycosis of pigeon-breeders have been established.¹

¹ There is a class of individuals in France whose profession is the feeding of pigeons ("gaveurs de pigeons"), and it was a matter of popular observation that many of these

Aspergillar pulmonary mycosis¹ also arises from other sources, many of them inexplicable; and besides appearing as a primary infection, it may be secondary to other diseases of the lungs, the association of pulmonary tuberculosis and this mycosis having been noted. It is not entirely clear how the fungus provokes its pathogenic effects. The production of toxins has not been proved, and many maintain that the morbid tissue-reaction is merely the result of a foreign-body invasion. It is more probable that, as in the case of actinomyces, the pathogenic aspergilleæ act both as foreign bodies and as producers of a mild toxin, to which the necrotic and leukotactic effects of their presence may be ascribed. Histologically the tubercles produced by these fungi resemble those of tuberculosis.²

The **Spheriaceæ** are ascomycetous fungi in which the spore-case or ascus is provided with an orifice for the escape of the spores. Most of the representatives of this order are saprophytes or are parasitic in other plants. The genus *Cordyceps* attacks certain insects; a related fungus, *Botrytis bassiana*, is the causative agent of the muscardin of silkworms, as Pasteur has shown. Certain species probably belonging to *Botrytis* have been found in human beings, as in a case of nasal catarrh by Schubert. Other spheriaceæ have been found in the auditory canal.

UNCLASSIFIED PATHOGENIC FUNGI.

Besides the fungi which have just been considered, the botanic relations of which are sufficiently well determined to admit of a system of classification, there is concerned in human diseases a series of microscopic plants the taxonomic position of which is uncertain. Some of these fungi have enough in common to be grouped together; but it is particularly with regard to their relations with bacteria and with the higher fungi just described that doubt exists. In many cases the lack of accurate data concerning the saprophytic life of these fungi is responsible for the difficulty. For the present purpose, however, only one course remains open; that is, to describe them together.

We shall first consider the **pathogenic ray fungi**, to which a number of organisms important in pathologic mycology belong, and which are characterized morphologically by a unicellular, branching, continuous or inter-

men were afflicted with a chronic pulmonary disease resembling phthisis. In examining the sputum from some of these cases, with the expectation of finding the bacillus of tuberculosis, small mycelial filaments were discovered instead, which by cultivation yielded a growth of *Aspergillus fumigatus*.

In this process of feeding ("gavage") of pigeons, a mixture of water and grain is insufflated into the bird's throat by means of a tube. In this manner direct contagion from the pigeon is rendered easy, though it is not certain whether the infection in man comes from the already diseased pigeons or from the particles of grain used in the feeding, which carry the spores of *Aspergillus*. The malady provoked by this infection takes a characteristic clinical course with some fever and emaciation, but it is chronic and not invariably fatal; in fact, some cases seem to recover entirely after several years of illness. The diagnosis is readily made by having in mind the occupation of the patient and by the discovery of the filamentous fragments of the fungus in the sputum. The organisms may also be recovered in culture or by the inoculation of animals, where a fatal aspergillus mycosis is produced, death resulting in three or four days in the pigeon after intravenous injection, or in six to eight days in the rabbit.

¹ See the monograph of Saxer (Pneumonomycosis aspergillina, Jena, 1899), and the paper of Pearson and Ravenel (*Proc. Path. Soc. Philadelphia*, new series, iii., 10, 1900).

² Oprùts and Moffitt (*Phil. Med. Jour.*, June 30, 1900) describe a pyemic process in a man, associated with a spore-forming mycelial fungus which exists as large round bodies in the lesions, but forms mycelium in cultures. A similar case is described by D. W. Montgomery (*Br. Jour. Derm.*, xii., 341, 1900).

rupted nonseptate mycelium, certain threads of which become spore-bearing. The individual filaments are quite straight, are bounded by a transparent membrane, and show a homogeneous internal structure during active vegetation. Sporulation is accomplished by a segmentation of certain of the mycelial threads to form conidia, and reproduction takes place from these spores or from fragments of the mycelium. True branching of the mycelial threads is a characteristic of these fungi. Various terms have been applied to the ray fungus group, the type of which is the organism of actinomycosis, and from the radiate threads of which the name is derived. Thus, they have been placed among *Cladothrix*, or so-called higher bacteria; they have been termed *Streptothrix*, from their twisted threads; *Oospora*, from their fancied resemblance to the *Oospora vulgaris* described by Wallroth; *Nocardia*, a noncommittal designation, after Nocard, who discovered one of the pathogenic species (that of a farcy-like disease of cattle); and *Leptothrix*.¹

It will be unwise, however, in describing individual members of the ray fungus group, to use the generic name *Actinomyces*, since this has not been fully sanctioned. The better plan seems to be to describe them under the specific names now commonly employed. In fact, it must be remembered that exact biologic data concerning a number of organisms in this group are still wanting, and that on further analysis some of them may be shown to be out of place in the ray fungus group.

Actinomyces bovis (*Nocardia* or *Oospora*), *Streptothrix actinomyces*, etc., are the terms by which the specific ray fungi of actinomycosis are known, which were first recognized and illustrated by Lebert in 1857. The disease in cattle was accurately described by Bollinger in 1877, and the human affection distinguished by Israel in 1882. There can scarcely be a doubt that several distinct species of actinomyces are capable of producing the clinical and pathologic picture of actinomycosis bovis and actinomycosis hominis, although it is impossible to define them sharply at present. As has already been indicated, *Actinomyces bovis* serves as the type of the ray fungi group, and, like most other representatives of its class, occupies an undetermined botanic position so far as its relation to other nonbacterial fungi is concerned. This indefiniteness is largely to be ascribed to lack of information as to the life history of these fungi under the saprophytic conditions in which they naturally exist.

As encountered in the tissues and secretions of infected animals, this fungus appears as tangled masses of threads, the ends of which make a kind of radiate figure or roset, and which are ordinarily visible in the form of small grains of a yellowish, red, or green color. At the extremities of the threads, particularly those of the periphery, pyriform or globular swellings are usually seen, while at other times nodular thickenings appear. The whole radiate mass is composed of this tangle of branching filaments constituting a mycelium, the filaments being sometimes composed of a succession of short rod-like structures. Originally it was considered that the bulbous extremities of these actinomycelial grains were spores; but this is not the case, though their exact nature is still undetermined, the most popular

¹ For a full discussion of the botanic position of these organisms, with an excellent bibliography, the student is referred to Hektoen's article, "The Classification and Nomenclature of the Ray Fungi," *Philadelphia Monthly Medical Journal*, November, 1899. To appreciate the confusion which has existed in the classification of these fungi, one should note the synonyms appended to the various species as described in some systematic work, as Blanchard's.

opinion being that they represent degenerative changes of the membrane bounding the terminal filaments. Cultures on ordinary media can be secured from these grains as they appear in the pus of actinomycotic lesions in man or cattle, although with some difficulty, since many of the masses are defunct. Growth is rather slow, but the surface of the solid medium ultimately becomes covered with a continuous furry layer, usually of a dirty white hue, but at times showing traces of yellowish, reddish, or black pigment. Gelatin is slowly liquefied. Ordinarily bouillon culture appears in the form of a submerged granular deposit on the side and bottom of the tube, but by certain manipulations a surface culture appearing as a velvety pellicle may be obtained. Here a process of sporulation may be observed, the aerial threads segmenting into a series of spheric or oval protoplasmic fragments, appearing in lines at the extremities of the projecting hyphæ. This production of conidioid bodies is the only process of fructification thus far observed among the ray fungi, and that it is a reproductive phenomenon seems undoubted from the facility with which new fungi develop from these "spores." A white surface layer on solid media is also significant of this mode of sporulation.

Actinomyces bovis passes its saprophytic existence principally upon cereals, and more rarely on certain grasses, where it probably flourishes as an oidium-like fungus comparable to the mildews. It is merely a facultative parasite, as must be evident from its inferior adaptation to this mode of life, being poorly equipped with destructive means like toxin-production, and also unable to find its way directly from host to host. Numerous recent observations leave no doubt as to the usual mode by which infection of man and cattle takes place, this being by contact with such grains as barley, rye, or wheat, or certain species of grasses. A particle of the barb of these cereals or grasses containing the ray fungi pierces the skin or finds its way into the respiratory or digestive tract, and from the traumatism which it provokes as a foreign body a nidus is made in which actinomyces grows.

Experimental inoculation with material from actinomycotic lesions or with cultures has given inconstant results. In most cases the reaction provoked by the inoculated fungus was nonprogressive, resembling that induced by an irritative, inanimate foreign body. Spontaneous infection is most common in the herbivora, especially cattle, but has been known to affect horses, swine, and dogs. It varies in its manifestations according to several modifying factors, such as susceptibility of the host, virulence of the particular species or variety of the fungus, nature of the organ or tissue attacked, and also according to the presence or absence of a mixed infection with pathogenic bacteria, which, in the case of the pyogenic cocci, is no rare incident.

Both an exudative and a proliferative tissue-reaction mark the invasion of the human organism by pathogenic ray fungi, the earlier and more frequent response being an exudate of a purulent character, later followed by the formation of granulation-tissue and scar-tissue. The reaction is a local one, and, compared with that of most other pathogenic vegetable organisms, a slowly progressive and mild one, due, no doubt, to the feeble or slightly toxic effects of the ray fungi. A round-celled infiltration, mostly of lymphocytes, is first induced, followed by the ingress of polynuclear leukocytes. Disintegration of the localized cells usually sets in early, with softening and the production of purulent foci. The outlying connective tissue responds to the irritation and a barrier of granulation-tissue surrounds the morbid area, and

in this tissue plasma-cells and mast-cells are abundant. Local extension is slow, seemingly dependent on the offshoots which grow in all directions from the original colony of ray fungi, and influenced by such factors as the nature of contiguous tissues, gravity, and the like. Phagocytosis, as in other infectious processes, is active about the foci of actinomycosis, and it is probable that vegetative portions of the infecting organisms are transported locally by this method, a supposition strengthened by the prevalence of degeneration among the cellular elements about actinomycotic lesions. Sometimes the production of new connective tissue is excessive, making neoplasms of considerable size, although the phenomenon is more common in cattle, where massive tumors of fibrous or osseous tissue mark the site of actinomycosis. At other times, either from the unusual chronicity of the disease or on account of the specific reaction to certain species of actinomycetes, a nodular process is set up, characterized by the proliferation of endothelioid cells, sometimes by giant cells, forming focal accumulations or nodules which tend to degenerate by caseous metamorphosis. At times both the exudative and proliferative phenomena may be seen in combination, and large fungous neoplasms with more or less suppuration are produced. In regions remote from large lymph-channels and vascular channels, the extension of the disease is usually slow; but both the larger lymph-channels and the blood-vessels may be invaded by the infective material, rapid metastasis being the result. This event is especially likely to follow the invasion of the larger veins, the lymphatic route being much less frequently selected.

Of the portals of entry for the actinomycetes, at least four are well known: the mouth and nasopharynx, the respiratory tract, intestinal tract, and skin (chiefly through wounds). At times it is impossible to discover the point of entrance (*cryptogenetic actinomycosis*). While infection is apparently possible through the direct transmission of actinomycetes or their spores through the medium of air, water, or soil, the more natural method is with particles of grasses or grain, on which the organisms pass their saprophytic existence, as carriers.

Streptothrix farcinica (*Nocardia* or *Oospora*) is the organism described by Nocard as the pathogenic factor in "farcin du bœuf," a nodular or tubercle-like affection of the superficial lymph-glands of cattle; nodules also occur in the viscera. The fungus appears as branching segmented threads joined in short sections, and Nocard claims to have observed the formation of conidial spores. Growth on culture media is in the form of a yellowish-white mouldy layer. It is pathogenic for guinea-pigs, cattle, and sheep, the mycosis usually taking the type of a pseudotuberculosis.

Streptothrix Forsteri is the fungus encountered in lacrimal concretions, which are largely composed of masses of the organisms. It has often been confounded with *Leptothrix*, especially *L. buccalis*, found as a coating upon teeth or as the agent of a pharyngomycosis. *Nocardia Hofmanni* and *N. Gruberi* are two species closely resembling the typical *Actinomycetes*, found as saprophytes, but also determined to be pathogenic for animals.

Nocardia asteroides (*Cladothrix* or *Oospora*) was discovered by Eppinger in 1890 in a cerebral abscess complicated with cerebrospinal meningitis, and appears as branching segmented threads, which are remarkable for the readiness with which they break into short quadratic fragments. The cultures are not distinctive, and the organism possesses no proteolytic property. Inoculations into rabbits and guinea-pigs produce pseudotubercles composed

chiefly of focal accumulations of leukocytes. The organisms obtained by Almquist, by Ferré and Faguet, and by Sabrazès and Rivière, from cases of cerebral abscess, resemble Eppinger's fungus. The same applies to a case of pleuropneumonia with subcutaneous miliary abscesses, studied by Rivière.

Streptothrix Maduræ (*Nocardia*) is the fungus of Madura foot, or mycetoma as Carter designated the peculiar disease of the feet and hands characterized by nodular foci, discharging a thick, fetid, puriform fluid, poor in pus-corpuscles, swelling of the affected members, and at times a necrosis of the bones. Peculiar yellowish or black granules found in the discharge were suspected by Ballingall in 1855 as being of parasitic origin, and this opinion was confirmed a few years later by Carter, who pointed out the resemblance of the grains to those of actinomycosis. Several instances of

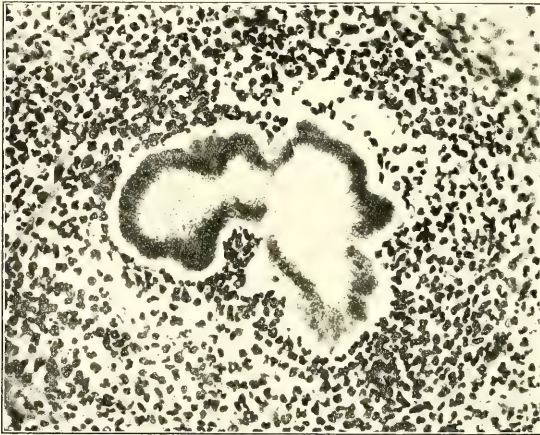


FIG. 98.—Mycetoma. Fungus surrounded by a dense accumulation of leukocytes. 300. (Dr. Hyde's case; from a photomicrograph.)

mycetoma have been observed in this country, principally in Texas. At least two varieties of the disease have been recognized by the color of the granules, the pale-yellowish or ochroid variety, and the black or melanoid variety.

Like those of actinomycosis, the ochroid granules of Madura foot consist of a mass of interwoven branching filaments or hyphæ radially arranged, making a mycelium such as seen in other ray fungi. These filaments are nonseptate, and the peripheral ones often show swollen or clubbed ends, though not invariably. Growth upon ordinary culture media occurs both at the room and body temperature, and the surface colonies on solids show a yellow, white, or even reddish color. Gelatin is not liquefied. In certain fluid media, like hay, straw, or vegetable infusions, this fungus grows especially well, forming a dense pellicle, from which the aerial hyphæ project,

the ends of which become sporogenous, giving rise to very resistant spores capable of propagating the organism.

The organism of melanoid mycetoma seems to be quite distinct from that just described, agreeing only in the formation of a dense radiate mycelium in the black granules. The filaments or hyphæ composing this mycelium are coarser than those of the ochroid fungus, more variable in size, and show both branching and lateral budding; they are also distinctly septate. On culture media the fungus grows rather slowly, producing a distinctly mouldy surface layer, from which aerial filaments grow in tufts. No production of conidia has been detected, the only approach to a process of fructification being a segmentation of some of the hyphæ in older cultures into a series of short segments. Wright, who obtained a growth of this organism, noted the formation of numerous black spheric granules in old growths, appearing in the midst of the mycelium and consisting of closely packed spheric or polyhedral cells, together with some short, thick, segmented hyphæ. The walls of these cells have a black appearance, and the granules seem to represent masses of interlacing, swollen, and much segmented hyphæ, and have been described as sclerotium. From the data thus far obtained, there seems to be little in common between the yellow and black fungi of mycetoma, and the latter seem quite remote morphologically from the ray fungi, having, as Dantec pointed out, closer affinities with *mucor* or *aspergillus* than with actinomycetes.

Histologically the lesions of Madura foot are chronic and granulomatous, with atypical arrangement of lymphoid, epithelioid, and giant cells. At times an inflammatory reaction predominates, with accumulation of polynuclear leukocytes; and cavities, filled with pus-cells, endothelioid cells, and the débris of cellular necrosis, may form around the fungus granules. A boundary zone infiltrated with lymphoid cells and plasma-cells may form, and dense granulation-tissue is sometimes produced.

Nothing is known as to the saprophytic habitat of the ray fungus of mycetoma, in which parasitism seems to be an accidental acquirement for which it is poorly adapted, as evinced by the local confinement and chronic course of the disease in man, and by the failure of all experiments looking to its pathogenesis for animals. It is even less advanced in parasitism than *Actinomyces bovis*. The mode of its entrance into human beings is not determined, though the malady seems to follow a wound in the affected region. A prick, and particularly one by the thorns of *Acacia arabica*, an Indian tree, has been held responsible by certain observers, a view not improbable from what we know of the mode of entrance of *Actinomyces bovis*, although apparently refuted by the appearance of Madura foot in localities remote from the region where this tree is indigenous. Possibly, as in the case of other ray fungi, the fungus of mycetoma infests several different species of higher plants.

Streptothrix pseudotuberculosis is the designation applied by Flexner to a branching filamentous fungus discovered by him in 1897. The fungal threads appeared chiefly in the form of convoluted masses, some of which, as they terminated, showed imperfect partitions tending to break them into short rods. No cultures were secured, and inoculations of the pathologic tissue containing the threads into guinea-pigs were without result. In the man from whom the specimens were secured at autopsy there was a diffuse caseous pneumonic consolidation of the lung resembling a tuberculous affection, the

resemblance being heightened by the presence of miliary nodules consisting mainly of epithelioid cells, some of which were necrotic. Similar nodules were present in the omentum and other parts of the peritoneal cavity. Fungi apparently related to *S. pseudotuberculosis* have also been described by Buchholz, Scheele and Petruschky, and Larkin and Norris, all obtained from human lesions.

Before dismissing the ray fungi, it is well to recall the fact that some authorities now propose to include in this group all the pathogenic bacteria which show true branching, like *Bacillus tuberculosis*, *B. diphtheriae*, and *B. mallei*. In this same category doubtless also belong the acid-proof filamentous fungi which have recently been found in atypical cases of human pulmonary disease or by animal experiments, like the timothy, cow-dung, and grass bacilli of Möller, the butter bacilli of Rabinowitsch, the tonsillar bacillus of Marzinowsky, and an acid-proof bacillus recently obtained by Rabinowitsch from a case of pulmonary gangrene.

Besides these more pronounced pathogenic thread fungi which we have just described under the ray fungi, there are several organisms of recent discovery whose affinities have not been fully established and which may be here mentioned only as a matter of convenience. Thus, there is the fungus described by Cazzolino as *Bacillus filamentosus*, and obtained from a subcutaneous nodule behind the ear and from a retropharyngeal abscess in a young woman, appearing to the eye in the form of minute yellow or red actinomyceloid grains, growing well on ordinary culture media, and pathogenic for guinea-pigs and house-mice, producing in these animals pulmonary congestion and focal hepatic necrosis. In the tissue from the primary point of infection in the woman, the lesion resembled that of actinomycosis so closely as to merit the name "pseudo-actinomycosis," and the fungus was disposed in radiate filaments with clubbed ends. By cultural methods considerable deviation from the typical fungus of actinomycosis was shown, especially by the absence of branching, by the production of swarms of bacillary or spirilla-like rods, and by endogenous sporulation. It resembles more closely the anaerobic "bacilli" of pseudo-actinomycosis described by Sawtchenko and by Krassnobazew.

Another of these unclassified fungi is the *Sporothrix Schenckii* (Hektoen), a filamentous, sporogenous organism showing true branching and budding; it was obtained by Schenck (1898), and later by Hektoen (1900), from cases of chronic subcutaneous abscesses of the hand and arm, running a clinical course like farcy. The resemblance of this fungus to the meager description of *Leptomitus epidermidis* has already been pointed out. In the infected tissues the organisms only appear as round or oval spores, not as filaments. They grow readily on ordinary media, and here a well-defined branching and budding mycelium of rather thick septate filaments is produced, from which spore-bearing or conidial threads radiate. The spores resemble yeast-cells and are able to reproduce the fungus. Experimental inoculations with the cultures were especially successful in guinea-pigs and white rats and mice, in which subcutaneous or intraperitoneal injections produced chronic circumscribed inflammatory and necrotic nodules accompanied by the formation of focal abscesses, closely resembling the lesions seen in the human being. This was more especially marked in subcutaneous injections in mice, in which the nodules coalesced and disintegrated, resulting in ulceration similar to that seen in patients.

In finally disposing of the unclassified pathogenic fungi, it is necessary to dwell briefly upon the organisms concerned in several parasitic cutaneous diseases (dermatomycoses). It will scarcely be profitable to go into minute details concerning these quite well-known fungi, or to attempt to describe the now considerable number of species differentiated by workers in this branch of mycology. Three of these cutaneous diseases and their parasites have long been known, viz., favus caused by *Achorion Schönleini*, tinea or herpes tonsurans by *Trichophyton tonsurans*, and pityriasis (tinea) versicolor by *Microsporon furfur*. Several subspecies of these three principal cutaneous fungi have also been described. The saprophytic existence of these fungi which in man induce affections more or less contagious is not determined, and their botanic position has not been established. The general characteristics of the dermatomycoses excited by them are a mild grade of inflammatory reaction, and hyperplasia of the epithelial elements of the skin. Scaly eruptions are in this way produced, some of which present characteristic colors. The fungi form extensive mycelia, which burrow in the superficial layers of the skin and along the hair-bulbs. In certain forms of tinea tonsurans, pus is produced along the roots of the affected hairs, or it may even affect the nonhairy portions of the skin, producing isolated pustules or purulent infiltration. The mycelial hyphæ of these fungi are septate, and all of them produce spores on special hyphæ resembling conidia. The organisms may be cultivated from their conidia on certain media, and reproduce simple or branching septate filaments which expand into the characteristic mycelia. Pyriform swellings appear on some of the threads, the significance of which is still undetermined. Some of these fungi have been successfully inoculated into animals, reproducing cutaneous diseases.

THE PATHOGENIC PROTOZOA.¹

Among the forms of animal life that have acquired parasitic properties are representatives of the lowest subkingdom, the Protozoa, a subdivision including those organisms which are unicellular in their fully developed state. The protozoa are minute single-celled organisms, existing either as independent individuals or as aggregations of similar forms.

Most of these animalcules are either free-living or saprophytic in their mode of life, and, compared with the fungi we have just discussed, relatively few of them are known to be parasitic in man. Of the few human protozoan microparasites, however, one particular class, represented by the

¹ Much of the literature on the pathogenic protozoa is to be found in the journals devoted to bacteriology and pathology, which have already been indicated. An elaborate systematic presentation of protozoa in general is to be found in Bütschli's *Protozoa*, Bonn's *Classen und Ordnungen des Thierreiches*, Leipzig, 1882. A more extended consideration of the pathogenic protozoa will be found in Leuckhart's *Die menschlichen Parasiten*, Leipzig, 1879; Blanchard's *Traité de Zoologie Médicale*, Paris, 1885; Braun's *Die thierischen Parasiten des Menschen*, Würzburg, 1895; Kruse's *Systematik der Protozoa* in Flüge's *Die Mikroorganismen*, Leipzig, 1896; Blanchard's *Parasites Animaux* in Bouchard's *Traité de Pathologie Générale*, tome ii.; Moniez's *Traité de Parasitologie*, Paris, 1896; Pfeiffer's *Die Protozoen als Krankheitsreger*, Jena, 1891; Behla's *Die Amöben*; Balbiani's *Leçons sur les Sporozoaires*, Paris, 1884; v. Waselewski's *Sporozoenkunde*, Jena, 1896; and Celli's *Malaria According to the New Researches*. Useful reviews upon various aspects of protozoan parasitology will be found in the *Ergebnisse der allgemeinen Pathologie* of Lubarsch and Ostertag; while in the English language the most exhaustive and valuable description of the malarial parasites in all the aspects presented by recent investigations will be found in the article "Malaria," by Marchiafava and Bignami, in the *Twentieth Century Practice of Medicine*, vol. xix., 1900.

organism of malaria, is of great interest and importance to pathologists, and it is not improbable that further knowledge will add to the list of pathogenic protozoa.

As to the place of these minute and chiefly aquatic animate forms in the organic scale, there has been some difference of opinion, since they approach closely the unicellular vegetable organisms and shade so insensibly into the multicellular animal forms as to make division difficult. In the case of those species with which the pathologist is concerned, however, no such difficulty arises, since these forms are far enough advanced in organization to make their animality undoubted.

Morphologically the protozoon exhibits a cell of varying shape, size, and structural complexity. This cell, which in mature forms is the animal itself, is composed of a protoplasmic interior, holding a nucleus well defined as such, or nuclear material dispersed throughout the protoplasm; while without, the protoplasm in all the higher protozoan forms is bounded by a definite external envelope, the cell-wall. Many protozoa are also provided with a dense external covering or shell, which may be soft and pliable or hard and calcareous. Locomotive organs, as cilia or flagella, are provided for many species. In the simpler representatives the protoplasmic mass composing the cell-body is undifferentiated, or at most composed of an outer clear portion (ectosarc) and an inner more dense portion (endosarc), this formless mass of living jelly constituting the entire organism; but in more advanced organisms, parts of the cell show a structural differentiation, some reaching that stage in which a definite aperture for food, another for excreta, and a distinction of the ends of the body exist.

The mechanism for obtaining food is generally simple, the protozoon merely enveloping the food particle by flowing its protoplasmic substance in such a manner as to surround and engulf the object. This mode of feeding is rendered possible by a kind of worm-like motility which the organism possesses, the so-called ameboid movement, by which it projects a portion of its substance in foot-like processes (pseudopodia), the bulk of the cell following by a curious forward flowing motion. In more specialized types, certain vibratile fibers or cilia develop a rhythmic motion, causing currents in the fluid medium by which food particles are drawn toward and into the food aperture. Certain vacuoles or spaces in the protoplasm serve to contain the food particles, while another system of vacuoles shows a kind of pulsation, appearing and disappearing at regular intervals, the so-called contractile vacuoles.

Reproductive phenomena in the protozoa take several distinct types, and even in a given species the character of the reproductive act may vary. Simple fission or direct constriction of the cell and nucleus of a mature organism into two new ones is the common asexual type. Sporulation is also frequently observed, the parent animalcule becoming enclosed in a dense wall (*encysted*), with or without sexual conjugation, and then dividing into minute protoplasmic particles taking a variety of forms, the so-called *spores*, which, on being set free under appropriate conditions, develop into mature organisms. Sporulation may be preceded by a fusion or conjugation of two apparently similar mature organisms, or a partial conjugation may occur in which the conjugating organisms only remain in contact temporarily until an interchange of nuclear material has been effected, then separate and multiply. Finally there is, even among these lowly animal

types, a distinct sexual process with well-defined male and female sex-elements and a process of fecundation or fertilization.

SPECIAL PATHOGENIC PROTOZOA.

Three classes of protozoa have representatives as human parasites: namely, (1) Rhizopoda, (2) Sporozoa, and (3) Infusoria.

Parasitic Rhizopoda.—The Rhizopoda (or Sarcodina) are protozoa which move about and feed by the aid of pseudopodia of various kinds, and reproduce by simple fission or budding. Most members of this class are provided with chitinous or calcareous shells. Only one of the four orders into which the rhizopoda are subdivided has been found as a human parasite: that is, the lowest or *Amœbina*, in which both naked and shelled forms are found; and of the genera into which this order is reduced, that of the simplest forms, or *Amœba*, contains the principal rhizopodal species of pathologic importance. As a genus, the *Amœbe* are characterized by their short, blunt pseudopodia. Most of them have contractile vacuoles and nuclei. Reproduction takes place by simple fission in the active motile stage, or by encystment and sporulation in the resting stage. These organisms are chiefly aquatic—fresh-water or marine—although some species are found in the earth.

The most important parasitic member of the genus *Amœba* is *Amœba coli* of Loesch, also known as *Amœba dysenteriae* from its association with this intestinal affection. Several species of ameba have been encountered in the human dejecta, apparently of no pathogenic moment; they have been found in association with other micro-organisms in diarrheal stools. The first exact description of intestinal amebæ was given by Loesch in 1875, who found them in the stools of a fatal case of dysentery. Somewhat later, Cunningham described ameboid organisms in the feces of cholera patients. Similar protozoa were noted by various observers, but it was not until Koch and Kartulis turned their attention to the subject that the causative relationship of these amebæ to tropic dysentery was suspected. This was in 1885–87, when several publications were made by these investigators, which were soon followed by a large number of confirmatory reports from various parts of the world, both in and out of the tropics.

As encountered in the dysenteric stools, *Amœba coli* is a large protozoon, a naked protoplasmic jelly from 8 to 37 mikrons in diameter, showing a clear outer ectosarc and a more dense and refractive endosarc. When alive and under favorable conditions of warmth it is actively ameboid, projecting one or two broad, blunt-ended pseudopodia, which at first consist of clear ectosarc, and into this the endosarc flows, imparting a progressive movement to the organism. The endosarc contains numerous fine granules and coarser bodies, among which red blood-cells, intestinal epithelial cells, and fecal particles may be recognized. One or more noncontractile vacuoles also appear in the internal substance, along with a vesicular clear nucleus in which a body comparable to a nucleolus may be detected in fixed and stained preparations. In the spheric, quiescent ameba, no differentiation of the protoplasm into endosarc and ectosarc is noted. A process of encystment is seen in intestinal amebæ, and Grassi has described the formation of minute bodies or spores which arrange themselves in the center of the cyst in a roset-like cluster, although this mode of reproduction has not been thoroughly substan-

tiated in the case of *Amœba coli*. Simple fission is the ordinary reproductive method.

This ameba is constantly found in the stools of a particular kind of dysentery, which, from its regular prevalence in regions such as India, Arabia, and Egypt, is known as tropical dysentery. It is endemic in these regions, though not exclusively confined to them, cases of spontaneous origin having been repeatedly noted in the temperate zones. Besides appearing in the stools, the organism lies in the submucosa of the colon, usually at the base of the ulcerative defects characteristic of the affection. In the pus of complicating liver and pulmonary abscesses, the ameba also often abounds. In spite of the constancy of its presence, however, the precise etiologic significance of *Amœba coli* is still unsettled. Many observers, of course, hold that it is solely and directly responsible for the dysenteric affection; but this is vigorously disputed by others, who call attention to the uniform association of pathogenic bacteria in the primary intestinal lesions of tropical dysentery, and to the impossibility of deciding how far pathogenic micro-organisms may be carried in the protoplasm of these protozoa, even when not otherwise transported. And there remains another difficulty in the way of a satisfactory demonstration of the specific pathogenicity of these parasites: that is, the practical failure of all attempts to secure them in pure cultures; so that experimental proof is wanting. Nothing is known as to the saprophytic habitat of the ameba; it is suspected that the organisms live in fresh water and effect entrance into human beings through drinking-water.

The *morbid effects* of the infection in which this protozoan parasite participates, either as the principal or as an accessory agent, are confined chiefly to the submucosa of the large intestine, where an edematous softening and necrosis mark the beginning of the disease. As the morbid process advances to the mucosa, this lining also becomes soft and necrotic, ultimately sloughing, and leaving the ragged undermined ulcers so characteristic of amebic dysentery. The amebæ first appear in the submucosa, and, when the process has advanced to the stage of ulceration, these organisms may be found in the material filling the ulcerative defect, in the regenerating submucosa making the floor of the ulcer, and also in the apparently unaltered submucosa remote from the principal lesion. In sections of well-fixed tissue containing amebæ, they may be readily recognized by virtue of their metachromatic staining reaction with thionin, used after a special process (Mallory), or by the use of toluidin-blue (Harris). Apparently the presence of the ameba is not capable of exciting a chemotactic inflammatory reaction, and where suppuration occurs it is usually ascribed to mixed infection with pyogenic bacteria, as Councilman and Laffeur have shown in their thorough studies of amebic dysentery. A moderate infiltration of lymphoid cells and occasionally a proliferation of large endothelioid cells are the usual reactions provoked by these organisms. It is still undetermined how these protozoan parasites find their way into the submucosa, where they first appear, without demonstrable lesions of the mucosa, the most probable view being that they penetrate through the intact mucosa from the contents of the bowel, evidently finding in the submucous layer the proper soil for their pathogenic activity.

Liver abscess, usually solitary, sometimes multiple, is the most frequent secondary lesion of amebic or tropical dysentery, and here the characteristic ameboid organisms are often, though not always, found alive and generally numerous in the material from fresh abscesses. In small beginning abscesses

the process is particularly a necrotic one, in which the parenchymatous cells of the focus are disintegrated with little or no inflammatory exudation; and even in the large abscesses the contents are not ordinary pus, but a puriform, chocolate-colored fluid resembling anchovy sauce and containing detritus and amebæ with few leukocytes. Two methods of transportation are believed to be operative in the production of amebic liver abscess: one by the portal venous route, the amebæ penetrating the venous radicles in the affected intestines; the other by direct penetration of the colon and passage across the peritoneal surfaces to the liver, rendered relatively easy by the close proximity of the hepatic flexure of the colon to the liver.

From the studies by Quinke and Roos, which were a continuation of those inaugurated by Kruse and Pasquale, it has been discovered that it is possible to reproduce an ulcerative colitis in cats, by rectal injections of material containing amebæ, either the dysenteric stools or fluid from amebic abscesses, or of material from apparently healthy persons after a saline purge. It appears, however, that not all examples of amebæ tested in this way are uniform in their pathogenic activity; and from the results of these experiments and a consideration of the morphologic characteristics of the organisms, the authors first mentioned have endeavored to differentiate three species of parasitic intestinal amebæ, as follows:

(a) *Amœba intestini vulgaris*, 40 mikrons in size, coarsely granular, pathogenic both for man and the cat.

(b) *Amœba coli mitis*, morphologically similar to (a), but pathogenic for the cat alone.

(c) *Amœba coli* (Loesch), 25 mikrons in size, finely granular, pathogenic both for man and the cat and provoking dysentery in both.

Among the nonpathogenic amebæ apparently living in a state of commensalism in the human intestine, several imperfectly classified species have been described; and in the oral cavity, especially in the tartar on the teeth, several observers have discovered ameboid organisms, although it is unknown whether these really represent protozoan species or are developmental stages of some plant form.

Amœba urogenitalis, Baelz, 1883, is the title of a rather large (50 mikrons), actively motile rhizopod, which was found in the bloody urine and in the vagina of a 23-year-old woman dying of pulmonary tuberculosis, who, shortly before death, developed hematuria and extreme vesical tenesmus. Morphologically this animalcule closely resembled *Amœba coli*. Baelz was of the opinion that infection occurred first in the vagina, probably through washing with dirty water, the urethra and bladder being secondarily invaded. Jürgens describes the bladder of a man in which he found mucous cysts filled with amebæ, although no symptoms directed attention to this condition during life. Kartulis found amebæ, smaller than those described by Baelz, in the bloody urine of a man suffering from vesical tumor; and Posner records a case of sudden chills and hematuria in a patient, in whose urine large ameboid organisms were present, along with renal cells and tube-casts. The attack was repeated several times after the subsidence of the first one, the urine being free from blood in the interval. Posner thought a direct causative relation could be established between the amebæ (which he believed to have travelled from the bladder to the pelvis of the kidney, there becoming encysted), and the urinary disease.

As having a possible connection with the amebæ found in the oral cavity, the cases noted by Flexner and by Kartulis may be mentioned. The first-named observer found small, actively ameboid organisms in the pus evacuated from an abscess beneath the chin, which followed the excision of a nodule beneath the gum of the lower jaw, an ulcer remaining after the extirpation. The lesion was encountered in an old man, and in the fetid pus various bacteria were also present. Kartulis found amebæ measuring 30 to 38 mikrons in diameter in the pus and in a piece of exfoliated bone from a fistulous opening into a tumor-like mass the size of an orange, situated beneath the lower jaw of an Arab. No distinction between an endosarc and ectosarc was noticeable in the first-mentioned organism; but in the one described by Kartulis these portions of the ameboid body were well defined, and blood-cells and pus-cells could be distinguished in the coarsely granular endosarc, together with vacuoles and a stainable nucleus.

Pathogenic Sporozoa.—It is rare indeed to find all of a large class of organisms exclusively parasitic in their manner of life; but such is the case with the second protozoan class, which are now to be discussed—the Sporozoa. So far as is now known, not a single representative of this extensive group of unicellular animal organisms is free-living. Many of the sporozoa are, however, innocuous parasites; but others are capable of exciting pathologic changes or inducing death in the host. With the possible exception of Cœlenterata, none of the animal subdivisions above protozoa are exempt from sporozoan parasitism. From the pre-eminently predatory mode of life, a high grade of adaptation to parasitism is to be expected; this is precisely what we find in the sporozoa. Many of them are so minute in the adult condition as to enable them to exist within the cells of their animal host, sometimes in numbers. Having no occasion to obtain food by foraging, the adult sporozoon is not ameboid, but in most cases is provided with a dense external cuticle. Nutrition is secured by direct absorption of the juices of the host. A pulsating vacuole, such as is seen in the ameba, is not found. Although strictly unicellular organisms, certain sporozoa show a remarkable cell differentiation—an adaptation for greater security in their parasitic habits. This is illustrated in the case of certain Gregarina, in which the unicellular elongated body is divided into two portions by a partition: the posterior one or deutomerit, and the anterior one or protomerit, which is drawn out and again partitioned to make two parts, of which the pointed terminal one is the epimerit; this is furnished with hooks or other apparatus for attachment to the tissues of the host. The method of reproduction which obtains among the sporozoa is that best suited to further parasitism, being a process of encystment and sporulation with the production of spores, generally very small and well endowed with dense external layers or shells, by the aid of which the stress of extracorporeal existence is long endured.

These organisms vary widely in size. There is one species of Gregarina, an inmate of the intestinal canal of the European lobster, which attains a length of 16 mm. in its adult condition, and the spore cysts of which in the lower intestine of its host are as large as the head of a small-sized pin. This *Porospora (Gregarina) gigantea* is one of the largest unicellular organisms known. On the other hand, exceedingly minute forms abound among the sporozoan species, some taxing the extreme range of microscopic vision; and it is by no means improbable that, as in the case of recently studied bacterial organisms, there may be sporozoan parasites the spores

of which, as they abound in the tissues and juices of the animal host, are entirely beyond the range of our present optical appliances.¹

There is a wide range of morphologic diversity among the sporozoa, and thus generic and specific distinctions have been drawn until this class of protozoan organisms has become a very numerous one. But in the life history of a given species the morphologic phases are also diverse, complicated, and in many instances but imperfectly understood; in view of which the classification of these, as of so many other micro-organisms, is difficult. On the whole, it is not surprising to find that considerable discord reigns among the writers occupied in this trying field of microparasitology.

It was for a long time believed that all sporozoa were asexual in their mode of reproduction, the only exception to a strictly nonsexual process being the conjugation between certain Gregarinae, which preceded encapsulation and sporulation. But recent discoveries controvert this notion, a remarkable sexual process with a high order of preparatory steps having been proved for certain Coccidia, and a more simple one for certain Hemosporidia, so that it now appears more than probable that further study will discover sexual reproduction as a prevailing phenomenon among these lowly forms of animal life; and when the reproductive stages of the various representatives have finally been worked out, an entirely new basis of classification may be secured, probably changing radically the system now in vogue.²

¹ It is perhaps opportune to recall in this connection that there is a series of human maladies with decided impress of an infectious nature, in which no parasitic agency has been positively demonstrated. For example, the acute exanthemas, the contagious nature of which has been known for centuries, like *small-pox*, *scarlet fever*, *measles*, *chicken-pox*, and exanthematous *typhus*, are classed among this group of morbid affections. *Rabies* is a still more remarkable illustration. Now the morbid anatomic and histologic analogies of these diseases are such as to suggest their identity with many well-known and positively determined microparasitic affections, and the biologic (clinical) phenomena which they exhibit are similarly suggestive. We are therefore forced, for the present at least, to place them in a category of infectious diseases the specific parasites of which still remain to be discovered. Since the bacteriologic era, all of these diseases have been studied by the same methods which have yielded such brilliant and positive results in a large class of infectious maladies, and many microbic organisms have been heralded as specific excitants; but even at this time there is no case in which a reasonable scientific conservatism allows acceptance of the claims of those who profess to have made these discoveries. The failure of bacteriologic methods in a class of diseases so obviously infectious has long since directed the thoughts of parasitologists in other channels, and many have looked to the unicellular animal organisms—the protozoa—in the hope of there finding the etiologic agents. For the exanthemas, at least, this view, first proposed by prominent bacteriologists like Robert Koch, seems entirely probable, especially when we recall how barren are the attempts to cultivate artificially or to inoculate successfully the parasitic protozoa, how extremely small many of them are, and how roundabout the means by which they often obtain access to the human host. With the suggestions offered from sources of such authoritative prominence, it is but natural that the field of protozoan parasitology as related to these particular diseases should have been well explored, and with the consequence that several observers profess to have discovered unicellular animal parasites in *small-pox*, *measles*, *chicken-pox*, etc., in the blood, in the organs, or in the cutaneous lesions—claims which, like those of L. Pfeiffer, are much too positive.

Among other diseases of obscure etiology, leukemia may be mentioned as one in which protozoan parasitism has been suspected, a view at present strongly urged by Löwit.

² The studies upon sexual phenomena among sporozoans which have attracted special attention are those by Simond, Schaudinn and Seidlecki, and by Seidlecki (from whose paper, "Etude Cytologique et Cycle Evolutif de *Adela Ovata* Schneider," *Annales de l'Institut Pasteur*, xiii., 1889, the following data are obtained), upon *Adela ovata* and *Coccidium* (*Eimeria*?) *Schneideri*, two coccidia infesting the intestinal epithelium of *Lithobius forcipatus*, one of the Myriapoda. These observations are extremely interesting, and have been carried to that stage of completion that makes them models for future work along this direction.

Adela ovata is, in the adult intracellular condition, a large ellipsoidal organism, from 40 to 50 mikrons in length by 16 to 22 mikrons in width. Its protoplasm shows an

Therefore, as has so frequently been the case with reference to other organisms belonging to the great group of microparasites, we are compelled

alveolar structure and uniformly distributed fine granules. The external portion of the parenchyma forms a cuticular membrane. A spheric nucleus lies in the center. Within the nucleus are distinguished a karyosome and several filaments, and chromatin granules also appear on appropriate staining. This, which is now known to be the adult female form (*female gamete*), attains its full size and then proceeds to undergo a complicated process of nuclear division by which the mother-nucleus disappears and a series of chromatin particles are diffused in the protoplasm, at first condensed, but soon expanding into star-shaped figures, the organism at the same time becoming globular and its protoplasm condensed. The chromatin stars move to the periphery of the cell and contract into a dense oval reticulum, while about each of them the protoplasm segments until a series of oval nucleated bodies are produced; these elongate, become separated, and, to the number of twenty or more, appear as slightly bent, sickle-shaped, nucleated filaments, which on final detachment are motile. These bodies, arising from the segmentation of the gamete, are the *macrogametes*; they escape from the cell in which the adult parasite lay, finding their way into the lumen of the intestine. By virtue of their motility and their falciform shape, these segmentation forms can again penetrate the epithelial cells of the intestine, thus bringing about a reinfection of the host. Arriving in the cell, the falciform body becomes oval and gradually assumes the adult condition, to repeat the process of division just mentioned. This *asexual mode* of reproduction continues for some time.

Now, besides this larger adult form, there is a smaller oval one, with more compact, non-vacuolated protoplasm containing several small brownish masses of pigment. Its nucleus is relatively large, the chromatin is condensed into a close network, and a large karyosome with several vacuoles lies in the center. By its smaller size, its granular protoplasm, relatively large nucleus, this *male* parent cell, or *male gamete*, can be distinguished from the one just described. It grows to full size, when a process of nuclear division with preliminary division of the karyosome and dispersion of the chromatin appears, the globular cell finally dividing into meridional sections, each of which contains a compact nucleus and fragments of pigment. These sections ultimately separate into crescentic forms, which are parent male cells or *microgametocytes* ("microgamétocystes"); they are endowed with extremely active motility, and, on escaping from the harboring cell of the host's intestine, they swarm about in the lumen, again entering epithelial cells to become adult and divide by the asexual process. From this it is apparent that *auto-infection* of *Lithobius forcipatus* takes place by the *asexual reproduction* of *dimorphic representatives* of *Adela ovata*, which may be differentiated as female and male; and, so far as this host is concerned, such asexual method of reproduction is sufficient for the parasite. But it will be evident that this process makes no provision for the perpetuation of the sporozoan species in event of the death of the host, nor does it provide a means for the parasite to infest other representatives of this species of Lithobiidae. For this contingency and to give rise to a well-endowed resisting stage, another means of reproduction is called into play; that is, a *perfect sexual process*, the product of which finds its way from the intestines of the host into the outer world, there prepared to await a favorable moment for again entering a new host.

The sexual phenomena observed in *Adela ovata* are remarkably complicated when it is remembered that this species is only a lowly protozoan organism. It happens thus: Some of the macrogametes, instead of again entering the cells of the host, remain in the lumen of the bowel, there to become fully developed forms. In like manner, certain microgametes remain free. So far as the female cell, macrogamete (or even *ovum*, as we may now call it), is concerned, it is prepared for the act of fecundation except for a *process of maturation* or ripening, which appears actually to occur even in this lowly form of animal life. Preceding the maturation, a microgametocyte approaches the macrogamete and fastens itself to one pole, then the nucleus of the macrogamete recedes either to the opposite pole or to the one against which the microgametocyte is applied, and soon expels a particle of chromatin which escapes from the surface of the coccidium. Meanwhile an important transformation is going on in the microgametocyte, the nucleus of which goes through a division process giving rise to figures somewhat like those seen in karyokinesis, even to the production of a chromatic particle between the receding masses of nuclear substance (believed to be analogous with the "Zwischenkörper" seen in metazoan cells), and finally four elongated, somewhat pyriform bodies, composed almost or entirely of compact chromatin, are formed. These are the male reproductive elements, the *microgametes*; or, in other words, the *spermatozoa*. In the living state they are highly refractive and motile, though non-flagellate. Only one of these microgametes now penetrates the macrogamete at the pole in which the remainder of the nucleus lies. When the ripened nucleus of the macrogamete adjoins the pole to which the microgametocyte was attached, one of the spermatozooids enters directly; but when the female nucleus lies at the opposite pole, the microgametes travel around the female cell to reach this point. Here we have a perfect act of fecundation or fertilization, preceded by reducing divisions of both the male and female sexual cells. And as in fertilization among higher animal forms, so here the male and female chromatin filaments can be identified for a short time in the fecundated cell.

to accept as only provisional many taxonomic features now applied to the sporozoa.

Of the several systems of dividing the class Sporozoa, that making six orders has been most widely accepted, and is as follows:

Order I., Gregarinæ, single-celled, round, oval, or elongated organisms, some of large size, as has already been noted. Some have unpartitioned cell bodies (Monocystidæ); in others the body is divided into two or three segments, of which the anterior becomes specialized into a proboscoidiform attachment-apparatus (Polycystidæ). Parasitic in invertebrates (Echinoderms, Annelids, Arthropods, and Vermes). Reproduction by spores, the germinal portions of which consist of falciform protoplasmic rods.

Order II., Myxosporidia, sporozoa the adult stage of which is characterized by the presence of nuclei originating by division, further by the power of ameboid movement and by the mode of spore formation, which takes place in definite transparent areas (pansporoblasts), and which is progressive, not being confined to the last stage of the life cycle; the spores always exhibiting two, and sometimes three, axes of symmetry and possessing a shell resistant to chemical reagents, one or more capsules (each inclosing a coiled filament capable of extrusion), and a single mass of sporoplasm.¹ Parasitic in several invertebrates and also among fishes, where they often work great devastation, and in batrachians (only two or three species) and in reptiles (crocodile?).

Order III., Coccidia, are principally intracellular parasites, choosing especially the epithelial cells of the intestinal mucosa, although at times lodging between the cells of the intestinal submucosa or in lymph-glands, liver, etc. They are round or oval bodies, germinating by falciform spores formed within the parent cell, which becomes invested with a protective envelope; this mode of asexual reproduction takes place within the infected cells of the host, but another sexual process takes place outside of such cells, the product of this act dividing into a series of sporocysts which are the resisting stage of the coccidia, through which it infects new representatives of the host species. Each sporocyst contains two or more crescentic germinal bodies (*sporozoites*), which, when set free in a new host, penetrate suitable cells and establish a new generation.² Parasitic in certain invertebrates, like molluscs and arthropoda, and in birds, reptiles, and mammals, including man.

Among the mammalian coccidia the species best known is *Coccidium*

Following fertilization the impregnated nucleus of the cell is carried again to the surface, where the chromatin network becomes more compact, elongates, and divides into two portions, with the appearance of two "Zwischenkörper" in the uniting filament. This division or segmentation is repeated, the protoplasm following, until a series of aggregated round cells with a bounding membrane is produced, which are the *sporocysts*. Finally, within each of these sporocysts the protoplasm condenses and divides into two small elongated, curved rodlets, each of which contains a nucleus; these are the *sporozoites*. Escaping from the original host, some of these sporocysts finally find their way to the intestinal canal of another like myriapod, where the two sporozoites are set free to commence a new cycle.

¹ This definition is from Gurley, "The Myxosporidia, or Psorosperms of Fishes, and the Epidemics Produced by Them." From *Report of the U. S. Commissioner of Fish and Fisheries*, for 1892. This article, containing a detailed systematic description of 102 myxosporidian species parasitic in fishes and batrachia, is readily accessible to American students and should be consulted by those who would look more closely into this extremely interesting class of parasites.

² This description of the alternate generations and complex life cycles of Coccidia is founded on the observations of Simond, Schaudinn, and Seidlecki, in a few species (see description, p. 305, footnote). In all probability it applies to coccidia as a whole, with modifications for the individual species.

oviforme, especially common as a parasite in the epithelial cells of the bile-ducts and liver of the rabbit. In its encysted state this organism is oval, 33 to 40 mikrons long and 15 to 28 mikrons wide, surrounded by a double-contoured dense capsule, within which is a coarsely granular cytoplasm which contracts into a central sphere, afterward dividing to form four spheres which become ellipsoidal, encapsulated, and which are sporocysts ("*sporoblasts*") ; in them are produced two nucleated falciform bodies with an enlarged knob-like end, the *sporozoites*. These sporocysts, as in other coccidia, are the resisting forms of the parasites, which develop in the extruded stools of one host to infect the food and re-enter a new one. Besides this mode of reproduction (which is probably sexual), *Coccidium oviforme* shows another (asexual?) reproductive process in which a parent intracellular coccidium (called "*Schwärmercysten*" by L. Pfeiffer, who first described the process) divides into a large number (eight to thirty-six) of small sickle-shaped motile spores, which swarm into the intestinal canal and from which reinfection of the host occurs. It was this phenomenon that in 1892 led R. Pfeiffer to venture the prediction that this species had two evolutionary cycles, one endogenous and the other exogenous, a prediction which has been fulfilled in the case of the coccidium *Adela ovata*, for example, as we have already seen.

In man, infection by *Coccidium oviforme* has been observed several times, although some of the accounts are of questionable authenticity. Gubler described the case of a man with enlargement of liver due to tumor-like nodules, which on autopsy proved to be cysts with caseous, semipurulent contents showing numerous oval bodies, which were at first regarded as distoma eggs, but which Leuckart thought to be coccidia. Somewhat similar cases of liver affection were reported by Dressler, Sattler, and Perls. Virchow noted a similar case in 1860, but thought the oval bodies to be eggs of *Pentastomum*. More recently Podwyszożki described extensive coccidiosis of the liver in four cases examined by him, but his investigations are of questionable value and not generally accepted as trustworthy. In Silcock's case the parasite was carefully examined, and it probably belonged to *Coccidium oviforme* ; it was found in the liver of a woman, who presented obscure typhoid-like symptoms before death ; at autopsy numerous caseous foci were found in the liver, which were identified as coccidial nodules. Haddon also reports a somewhat similar case in which coccidial nodules were scattered in the peritoneum, omentum, liver, kidneys, spleen, and pericardium.

Another species, *Coccidium perforans*, also found in the rabbit, has also been apparently identified in the stools of human beings. The organism was found in the feces of a mother and her child, who had both been suffering from a chronic diarrhea.

Coccidium bigeminum, found by Stiles in the intestinal epithelium of the dog, has been detected occasionally in the intestines of man.

Several cases of coccidiosis of the kidneys and ureters due to undetermined coccidia have been described. In a purulent pleural exudate obtained by puncture, Künstler and Pitres also found coccidia-like bodies.

Order IV., **Sarcosporidia**, are elongated, relatively narrow organisms, the habitat of which is between the muscle-fibers or muscular fascia of a number of vertebrate animals, including man. As "*tubes of Miescher*" or "*of Rainey*" they have long been known, having been described in the domestic

mouse by Miescher in 1843, and in swine by Rainey in 1858. The adult form presents rounded or pointed ends and attains a varying length in the different species, some of which are remarkably large for unicellular organisms. Reproduction takes place by a process of sporulation in which great numbers of reniform or falciform spores are produced. These are considered as equivalent to the sporozoites of *Coccidium*, but the life cycle of the sarcosporidia has been but imperfectly worked out, and nothing is known of the mode by which infection occurs. L. Pfeiffer believes an intermediate host is necessary to transport the sporozoites.

Lindemann and Rosenbergs record cases in which sarcosporidia-like masses were found in the human heart. The observations are imperfect. A more probable case is that reported by Kartulis, who found Miescher's tubules in the abdominal muscles and in the abscess-cavities of a man who died of multiple liver-abscess and abscess of the abdominal wall; but even here the identity of the bodies described as sarcosporidia is doubted.

Order V., **Microsporidia**, are minute sporozoa infesting the epithelial cells or muscles of arthropoda particularly. They are generally encountered in the spore stage, invested with a thick shell which opens to give exit to an ameboid body; this finds its way into epithelial cells or other favorable sites, there to enlarge, encapsulate, and divide into numerous small spores by which auto-infection of the host is produced. These organisms are particularly notorious as the cause of pébrine disease of silkworms, having worked sad havoc to the silk industry of France and Italy by inducing extensive epidemics. Pasteur, who investigated this disease, found that the eggs of an infected female silkworm conveyed the microsporidian spores to new generations, and he suggested a satisfactory mode of prevention, consisting in the examination of the eggs and the destruction of those found infected.

Order VI., **Hemosporidia**, include the most important protozoa parasitic in the human being, viz., the organisms of malarial fever. It is a large sporozoan family of blood-parasites, as the name indicates; that is, of parasites which pass at least one stage of their existence in the red blood-cells of certain vertebrate animals, among which are numbered reptiles, amphibia, birds, and mammals. At the present moment it is important to emphasize the statement that the hemosporidia pass but *one stage* of their life cycle in the blood of a vertebrate host, for, in several of the members of this order infesting warm-blooded animals, it has been proved definitely that the parasites have *another life cycle*, passed in the body of some insect. As we have already seen in the case of *Adela ovata*, and as is suspected to be the case in *Coccidium oviforme*, the hemosporidia of warm-blooded animals, at least, have an alternation of generations, with this important difference: that whereas the second life cycle of the designated coccidia is extracorporeal, that of the hemosporidia is intracorporeal—in the body of an intermediate host.

Several attempts have been made by zoologists to classify the hemosporidia thus far discovered, but an unobjectionable system has not been found; and with the mass of new facts that are now accumulating with reference to the complete life history of this group of organisms, a new system is in process of construction. It appears more to our purpose, therefore, to pass over this phase of the subject and to describe the individual hemosporidian organisms, particularly those of direct or indirect importance in

human pathology. To this end, we shall consider two subdivisions: (a) hemosporidia of birds, and (b) hemosporidia of mammals.

Hemosporidia of Birds.—In discussing these organisms, at first sight belonging strictly to the domain of comparative pathology, a word of explanation should be offered. It is chiefly through the data gained in this field that our knowledge of the malarial organism of man has been enriched, and the organisms concerned in these avian infections are so readily accessible for study and so characteristic in their biologic phases that every student in this field of pathology should personally verify the facts already gathered, either as a preparation for or sequence to the study of human malaria.¹

Among the early communications relative to the organisms now comprehended in this sporozoan order was one by Gaule in 1880 upon certain hematozoa of the frog and turtle, which he styled "*Blutwürmchen*," without appreciating their parasitic nature, which E. Ray Lankester was the first to note in 1882, calling the cytozoon of frogs' blood *Drepanidium ranarum*. Lankester had already recognized these worm-like bodies in frogs' blood as early as 1871. A systematic and fruitful study of this organism and of related forms in lizards, turtles, frogs, and birds was soon after made by Danilewsky, who established a separate species in the turtle, at the same time recognizing the affinities of these hemocytozoa with the sporozoa. With the hemosporidia of the cold-blooded animals we will not be concerned, only remarking that they differ from those of birds in the absence of pigment, and that, while they are the members first recognized in this order, their life history is by no means so well elucidated as that of more recently discovered forms.

Among the several communications dealing with the hemosporidia of birds, those of Labbé must be especially mentioned, since he carefully studied the organisms of avian blood and distinguished two forms of parasites which he regards as genera, one of these being designated *Halteridium*, and the other *Proteosoma*. But one species of each genus is thus far known. The developmental phases of both these organisms, a brief outline of which follows, have been quite well worked out. Several avian species serve as hosts for these hemocytozoa, and of those indigenous to the United States may be mentioned the crow, blackbird, English sparrow, song sparrow, and the great horned owl.

Proteosoma Grassi is the irregular form of hemocytozoon of birds, characterized by its indefinite shape and particularly by its position in one end of the nucleated red blood-cell of its host, where, on attaining a sufficient size, it gradually displaces the nucleus of the erythrocyte, pushes it to one pole of the corpuscle, and causes it to lie almost at right angles with the long axis. It first appears within the infected cell as a minute, colorless, refractive, nonameboid body, which rapidly increases in size, at the same time showing particles of black pigment in its parenchyma, derived from the hemoglobin of the erythrocyte. Attaining a size about equal to half that of the red blood-cell, the organism divides into a number of small round bodies, the segmentation being preceded by collection of the pigment

¹ The papers by MacCallum and Opie (*Jour. Exp. Med.*, iii., 1898) and one by Koch ("Ueber die Entwicklung der Malaria-parasiten," *Zeitschr. f. Hyg. u. Infektionskr.*, xxxii., 1899) may be consulted with profit by those interested in the various phases of comparative hemosporidian investigation.

into the center of the now spheric organism, and the appearance of peripheral indentations giving the intracorpuseular body somewhat the appearance of a roset. From five to twenty small bodies with a circular outline result from the segmentation of the mature parasite. The red blood-cell decolorizes, assumes a roundish shape, its nucleus swells and becomes more round, and finally the shell of the corpuscle that remains bursts, and the young proteosoma are set free. Appropriate staining by Romanowsky's method reveals a nuclear chromatin mass in the parent organisms and a division of this nuclear substance during the segmentation, furnishing each of the young forms with a particle of chromatin. The full life cycle of the young proteosoma has not been followed, but from analogy it is quite justifiable to look upon it as equivalent to the pyrogenetic cycle in human malaria and to conclude that these bodies are the agents of autoinfection, invading new red blood-cells to mature and segment as their ancestors did.

Besides the organisms that divide in the blood in the manner just described, this hematozoon appears in another form—that of somewhat larger nonsegmenting bodies with disseminated pigment. Celli and Sanfelice have considered these forms analogous to the crescents of human malaria, and Opie has observed them to become flagellated in birds' blood. From what we shall learn of the significance of the crescents in human malaria, it is highly probable that the larger nonsegmenting forms are of the same nature.

It is evident that the process of intracorpuseular segmentation and the production of new groups of young parasites insures their perpetuation in the individual host, but not beyond. This is an imperfect parasitic adaptation not in keeping with what occurs among parasitic forms generally. Some means for preventing extinction must exist, for it is well known that these hemosporidia persist and that they infest large numbers of the host species. This is about the aspect that the problem of hemosporidian parasitism presented, both as to the hemocytozoa of birds and those of human malaria, when new light came through studies on the proteosoma, which has illuminated the whole subject of etiology of hemocytozoan infections. For it was discovered that in the case of the proteosoma of sparrows, besides the evolutionary phase completed and repeated in the birds' blood, there was another completed in an insect—the gray mosquito (*Culex pipiens*). This second cycle, experimentally studied by Ross, marked the new era in hematozoic investigations which has already been so profitably turned to account in the case of human malaria. He found that proteosoma could be carried from an infected to a noninfected sparrow by the agency of the gray mosquito. By causing these insects to bite an infected bird, it was found that new pigmented cells made their appearance in the stomach- (mid-intestine) walls of the mosquito, and not in the stomachs of mosquitoes nourished on the blood of healthy birds. By studying from day to day the mosquitoes which were fed upon blood containing proteosoma, it was found that the peculiar pigmented cells became encysted, and that their substance ultimately divided into an enormous number of delicate filiform bodies which, on the rupture of the mother-cyst, became free and found their way into the body-cavity of the insect. Some of these filaments (germinal rods) made their way into the salivary poison-gland of the mosquito, which, if the insect was permitted to sting a healthy bird, infected the latter with proteosoma. The ordinary period for the fulfilment of this cycle in the mosquito, from the

sucking of the infected blood to the appearance of germinal rods in the salivary gland, was found to be eight days. These observations made by Ross have been fully confirmed, especially by Koch, who rigorously repeated them; and it is now thoroughly established that the significance of the phenomena witnessed here is the same as that in human malaria, even to the processes of a sexual nature that mark the inauguration of the second life cycle. Of these we shall learn more definitely in connection with *Halteridium* and the hematozoa of malaria in man.

Of the other principal hemosporidian parasite of birds (*Halteridium* of Labbé), we know less as regards the second evolutionary stage of existence. In the blood of infected birds it appears first as a small, round, clear body lying at the side of the nucleus of the red cell, soon ingesting pigment, and growing to fill one side of the corpuscle, without seriously displacing the nucleus; but elongating parallel with the long axis of the oval corpuscle, and curving its ends around the nucleus. After attaining its maximum size the halteridium becomes spheric, causes one side of the red cell to protrude and finally to burst, setting free the round pigmented parasite. Multiplication by a process of segmentation such as noted for proteosoma has not been seen in this parasite, although the double or multiple infection of the red cell in severe cases is likely to be mistaken for such a process. Having become free in the blood-plasma, the mature halteridium, after a short period of rest, shows a violent agitation of its pigment and suddenly projects several long filaments from its periphery, which whip about actively. This is the formation of flagella; the whips are flagella, and the phenomenon is identical with that witnessed in the hematozoa of human malaria. Soon these flagella become detached and swim about in the plasma. Up to this stage the process of flagella formation in halteridium had been often seen; but it remained for MacCallum to carry the observation a step further and to place the correct interpretation on this process, both as relates to the hemosporidia of birds and to those of mammals. Carefully studying the halteridium in crows' blood, MacCallum distinguished two types of mature halteridium: one larger, more granular, and quiescent, never becoming flagellated; the other smaller, hyaline, and more active, producing flagella. Watching these two forms in fresh preparations, he saw one of the flagella, set free from a hyaline form, advance to a granular form and penetrate it. This operation MacCallum correctly interpreted as an act of fecundation, considering the quiescent organism a female element, and the hyaline flagellated one a male; thus was the first actual observation made of sexual phenomena in the hematozoa. Applying the biologic nomenclature to these forms, the large quiescent organism is the female gamete or *macrogamete*, the more active smaller one the male gamete or the *microgametocyte*, while the flagellation is a process of spermatogenesis, the individual flagella being male copulative elements, spermatozoa, or *microgametes*; and the final act is one of fertilization. In the case of halteridium the product of this fecundation soon becomes an elongated, motile, worm-like organism, the so-called "vermiculus" of Danilewsky, the exact significance of which is unknown, although it is believed to be a resisting form of the parasite, by which it may enter upon its second life cycle.

Beyond the phenomena seen in the birds' blood, just briefly described, nothing is known of the life history of halteridium; that is to say, nothing is at present known of the mode by which the parasite is carried from bird

to bird, nor is it clear how auto-infection occurs. Evidently some intermediate carrier among the insects must be called upon, for the infection is extremely widespread among birds of certain species, as the crow, where every individual, from fledgling to adult, of a series examined from a given locality, has been found infested with halteridium.

Hemosporidia of Mammals.—Among the hematozoa positively recognized in a parasitic role in mammals, two are of particular interest to us, viz., (1) the hematozoon of Texas fever, and (2) the hematozoa of malaria.

The Hematozoon of Texas Fever.—This is a nonpigmented, endoglobular, actively ameboid organism discovered by Theobald Smith in cattle affected with Texas fever: a malady characterized by malarial manifestations, as fever, anemia, and hemoglobinuria, and often working great devastation to the cattle industry of southern countries, where the disease is endemic. The parasite is a pyriform organism, often appearing in the red blood-cells in pairs, hence the name *Apiosoma* (*Pyrosoma*) *bigeminum*, applied to it by Smith. Free forms of the organism are also found in the blood-plasma, and Celli and Santori have distinguished two forms: a larger one with more pronounced ameboid movements, and a smaller one which moves *in toto* within the red blood-cell. The reproductive phenomena in this hemosporidium have not been thoroughly worked out, although Hunt claims to have found segmenting bodies in the capillaries of the endocardium.

The feature of most importance concerning this parasite, and one which had a marked influence in directing investigators into new fields of inquiry, was the discovery by Smith and Kilbourne of the intermediate host of Texas fever, the so-called cattle-tick (*Boophilus bovis*), a blood-sucking arachnidian insect infesting the skin of cattle. Exhaustive and apparently incontrovertible experimental studies have shown that this insect is the sole and active agent in transmitting Texas fever, and that the female tick, ingesting infected blood, permits the parasites to pass through her eggs to the larvæ, which, attaching themselves to healthy cattle, provoke the disease. Observations as to the phases presented by the parasite in the new host are entirely lacking; still, there is no disposition to dispute the correctness of Smith's conclusion. This most important pioneer work in the field of microparasitology was made between 1888 and 1892.

The Hematozoa of Malaria.¹—There is little reason to doubt that the specific parasite of the malarial fevers was seen by several observers before

¹ With the mass of information that has accumulated relative to malaria in its various phases, and more especially concerning the biology of the malarial parasites, no brief discourse, such as this must necessarily be, can do justice to the subject. It is therefore urged that more exhaustive treatises be consulted to fill in the numerous gaps, especially as to the details, that exist in this sketch. For this purpose the work by Marchiafava and Bignami, already referred to, should be studied. It presents an extensive bibliography, in which all the more important treatises and monographs on malaria are indicated. Information concerning the mosquitoes of the United States, which now becomes an important matter to the American student of malaria, may be obtained in the publications which the United States Department of Agriculture, Division of Entomology, is issuing to meet the demand. The technic of malaria investigation, and especially the Romanowsky staining method, which has given valuable information concerning the structural details of these and other protozoan parasites, are discussed in the current journals devoted to parasitology and pathology.

To the student of this fascinating branch of scientific investigation, it will be almost superfluous to point out again the desirability of personal, practical verification of at least some of the data already obtained: such, for instance, as might readily be done by studying the halteridium in the blood of the crow, and there witnessing the various phases of the parasite's behavior, including the wonderful phenomenon of fertilization.

Laveran definitely decided in 1880 the true nature of the peculiar bodies in the blood of persons suffering from malaria. This acute investigator was especially impressed with the parasitic character of these bodies when studying the flagellated organism, and in his early publications he differentiates several morphologic variations in his *Oscillaria malarie*, including the round, ovoid, crescentic, and flagellated, although undecided as to the intracorporeal habitat of those peculiar to the red blood-cell. It was Richard who determined that the small nonpigmented bodies were contained in the substance of the erythrocytes, and not upon their surface, as Laveran believed. Among the pioneers in the field opened by Laveran's work, for several years unnoticed, Marchiafava and Celli are particularly prominent, since they extended in several important directions the knowledge already gained, and began the studies upon malarial lesions traceable to the havoc wrought by the parasites in the blood. Among the host of capable investigators who have since contributed to this important subject, individual mention is impossible in this place, although credit is especially merited by the Italian investigators who have so materially advanced this line of inquiry. In America, the workers in the Johns Hopkins Hospital, under the inspiration of Osler, have contributed liberally to our fund of information.

The exact zoologic position of the hematozoa of human malaria has not been indisputably settled, although most authorities now agree in including them among the class Sporozoa and order Hemosporidia, with the several hematozoa of lower animals. Labbé, however, divides these blood-parasites into two orders: (1) Hemosporidia, and (2) Gymnosporidia, placing the human malarial parasites in the latter order. It will scarcely be profitable to discuss other systems which have been proposed; but it is important to know that, as judged by their morphologic, reproductive, and pathogenic manifestations, the hematozoa (plasmodia) of malarial fevers in man can be sharply divided into at least three groups. Whether this division is to be regarded as of generic, specific, or only of varietal value is not determined; but for practical purposes and for didactic presentation it must be recognized. According to this classification, which has its origin in the clinical manifestations of the malarial fevers affecting man, we may distinguish: (a) the *Estivo-autumnal Hematozoa*, (b) the *Tertian Hematozoa*, and (c) the *Quartan Hematozoa*.

Even among these three groups, and particularly in that of the estivo-autumnal (summer-autumn) class, it is highly probable that several varieties of parasites are found; but for present purposes this grouping suffices. As has been said, it is founded primarily upon clinical manifestations exhibited by the patients suffering from malaria, which disease we now know to be directly and solely dependent upon the presence and multiplication of hematozoa in the red blood-cells; to these hematic parasites may be charged the intermittent fever and the anemia of malaria. At present we know that the cycle exhibited by the parasites in the human host is only one in its evolution, the others being completed in a second host—in this case an insect. In the human host, however, the parasite undergoes a complicated metamorphosis consisting in growth, reproduction, and renewed infection of the special cells which furnish its habitat—the red blood-corpuscles. To one of these metamorphoses, endoglobular multiplication, the fever of malaria is charged. In one group of malarial hematozoa this reproductive phase reaches its height in two days, marked by a fresh paroxysm of fever every third day;

these are *tertian hematozoa*. In another group the reproductive cycle is completed in three days, fever appearing on each fourth day: *quartan*



FIG. 99.—1-22, Developmental forms of the common tertian malarial parasite (Mannaberg) (Figs. 17 and 18 after Thayer and Hewetson); 23-29, hydropic, degenerated, disintegrating bodies; 30, flagellate body; B, schematic sporulation of the tertian parasite (after Golgi).

hematozoa. That such regular clinical paroxysms should occur, with comparative freedom from disease in the interval, as is the case in the regularly

remittent malarial fevers, it is evident that practically all of the vast number of parasites in the blood must reach the reproductive or "sporulation" stage simultaneously. This is precisely what occurs. In still another group of organisms, however, the reproductive cycle is irregular, infection by them occurring in the summer and autumn in temperate climates: these are the *estivo-autumnal hematozoa*. Two groups of a single kind of hematozoon may be present in a given patient, reaching the stage of multiplication at different periods; hence the modifications of the tertian and quartan remittent fevers familiar to clinicians.

Many of the morphologic and physiologic features of the various malarial hematozoa are quite similar, at least during the fever-producing or "pyretogenic" phase of their existence in man. They first appear in the red blood-cells of the host as small, clear, ameboid bodies, which, as they increase in size, procure their nourishment from the harboring cell, whereby they convert the hemoglobin into pigment, which finds its way into their substance. The amount and disposition of this pigment differ somewhat in the three types of hematozoa, and this is true for the motility of the pigment granules in the ameboid body. Thus in the regular tertian parasite, which has an obscure outline and is actively ameboid, the pigment is abundant, in fine granules diffused through the parasite, and usually shows motility. In the quartan parasite the pigment particles are longer and nonmotile, and the outline of the parasite (which is larger and more sluggish than the tertian) is clear. The estival parasites never attain the size of the other types; they tend more commonly to assume an annular or discoid form, and the fine granular pigment is arranged about the periphery of the organism and is rarely motile.

All three types of the malarial plasmodium, after attaining a certain size, multiply in the enclosing red blood-cell by a process of fission, an operation equivalent to sporulation, as already mentioned in connection with sporozoa, the products of this fission being known

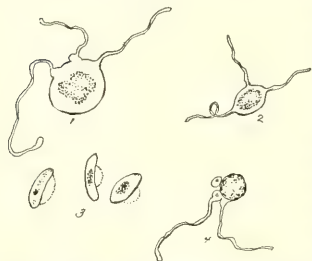


FIG. 100.—Crescentic and flagellated forms of *plasmodium malarie*: 1, flagellated form of tertian fever; 2, flagellated form of quartan fever; 3, crescents; and 4, flagellated form of estivo-autumnal fever (after Thayer and Hewetson).

here as *Gymnospires*. These fission products differ in the three types also. In the tertian parasite they number 15 to 20 and are smaller than those of the quartan, of which 6 to 12 are produced. Each quartan gymnospire shows a shining, highly refractive sphere, the *nucleus* or *nucleoliform* body, inconstant in the young tertian. In the estivo-autumnal type the spores are much smaller than in the tertian. During the fission of the mature endoglobular parasites, peculiar figures are produced, resulting from the radial direction of the

lines of segmentation; but these figures, which also differ somewhat in the three hematozoan varieties, agree in their general roset-like appearance, the larger ones of the quartan having been likened to a sunflower or a daisy with its expanded petals. At the completion of fission in these endoglobular parasites there remains a central portion, consisting principally of black pigment, the so-called "residuum of segmentation."

There is a further general resemblance between the bodies of the pyretogenic cycle in the three types of malarial parasites, in regard to the nucleus and the mode of nuclear division which takes place during fission. These characteristics have been only lately noted, and owe their recognition to the Romanowsky staining method, in which methylene-blue and eosin are mixed in definite proportions to produce a stain that colors the nuclear chromatin reddish or purple, and the cytoplasm varying shades of blue. After this procedure applied to properly fixed specimens of malarial blood, the mature intracorpuseular parasites have each a vesicular nucleus provided with one or more particles of chromatin. About the nucleus is the mass of cytoplasm with its black granules of pigment (melanin). The chromatin increases in amount as the parasite matures, and, at the moment of segmentation or fission, goes through a process of division roughly comparable with the karyokinesis of ordinary animal and vegetable cells, the isolated masses of chromatin being disposed in such a manner that the bodies resulting from segmentation of the parasite—gymnospores—form around the chromatin particles, each receiving its share.

So far our attention has been centered on only one phase of the life history of the malarial parasites: that passed exclusively in the body of the principal host—man. In the natural course of events the process just described repeats itself indefinitely, and is in reality a method of oft-recurring auto-infection, in which certain parasites mature, destroy a definite number of red blood-cells, reproduce themselves in multiple in the form of naked spores, these spores again invading new blood-corpuscles to repeat the series. As in the case of the proteosoma of birds, already discussed, no provision is made for the perpetuation of the malarial parasites—none for infection of other human beings; for it has long been known that malaria is not directly contagious. Here it was that all investigations came to a standstill until recently; and the significance of the irregular forms of malarial parasites, which are now to be described, was entirely conjectural.

Besides the forms of the pyretogenic cycle, each type of the malarial hematozoa exhibits others which, varying considerably in the different types, agree in that they do not multiply by fission in the host's blood and do not again infect blood-cells. For a long time these were called "sterile" forms, from their failure to multiply and also because they were finally seen to degenerate and disappear in the human blood. They are sterile in the organism of the principal host, and, failing to find the proper exit, they die; but this is not their natural destiny. In appearance, these sterile forms differ from those of the fever-producing cycle, and some of them are highly characteristic. They are, when spheric, generally larger on attaining their full size than the red blood-cells which harbored them, and larger than the forms multiplying by fission. They do not segment like the fission forms of auto-infection. Instead, when examined with the microscope in fresh preparations, some of them become flagellated by a process analogous to that already described for halteridium, the flagella finally becoming free and swimming in the blood-plasma. Other spheric forms never become flagellated. The exact morphologic significance of the various "sterile" forms of the tertian and quartan fevers has not been fully determined as yet; but in the case of the hematozoa of estivo-autumnal malaria, the sterile forms are well known during the greater part of their life history because of their characteristic semilunar or crescentic shape. Such *crescents*, first appearing in the

erythrocytes of blood-preparations from summer-autumn fever, then escaping to lie in the plasma, and finally contracting to assume an ovoid shape, either forming flagella or not, have long been known; and from their morphologic peculiarity and the impossibility of tracing their further development in man, they have always been objects of conjecture.

Sexual Phenomena.—We are now prepared to attempt an interpretation of some of the biologic characteristics of the malarial hematozoa. So far as the agents of auto-infection (of the pyretogenic cycle) are concerned, it is evident that they can only be regarded as asexual forms; that is to say, from the moment of entrance of the young ameba into the corpuscle to the time it reproduces its numerous progeny, which become free to repeat the cycle, no operation of a sexual import has been called into play. But the case is different in the sterile forms, certainly in the case of the crescents of estivo-autumnal malaria; for here MacCallum has seen an exact repetition of the process observed in halteridium, which was interpreted as an act of fertilization. He saw the crescents in the freshly removed blood from a case of human malaria quickly assume the ovoid shape that is peculiar to them when examined by the usual methods; some of the forms remained quiescent, others showed active pigmentary motion and suddenly projected flagella. The flagella soon became free and approached a quiescent form, into which one of them penetrated, the rest being refused admission. No particular change was noticed in the fertilized form. Here again we have evidence of a sexual process with the usual biologic significance: a process in which two forms participate—one male, the other female—the male cell or *microgametocyte* undergoing a process of spermatogenesis with resulting spermatozoa or *microgametes*, these microgametes fertilizing the female cell or *macrogamete*. When Romanowsky's stain is employed to study the forms concerned in these sexual phenomena, it is found that the nuclear chromatin of the parasites comports itself in a manner analogous to that seen in the sex-cells of higher animal forms. Thus far no maturation of the macrogamete has been observed; though, judging from what has recently been seen in the case of *Adela ovata*, it may be predicted that this will probably be found. However, during flagellation, the chromatin of the microgametocyte undergoes a reducing division, the result of which is to provide at least some of the flagella or microgametes with a long filament of chromatin.

So much for what is known of sex phenomena in the summer-autumn hematozoa, as actually witnessed. It has only recently been established that the tertian and quartan parasites go through a process similar to that just mentioned. Flagellation has been repeatedly seen in both these forms, and Romanowsky's stain determines that here also the chromatin of the parent cell is disposed so as to endow the flagella with nuclear material.

The Intermediate Host.—How is malaria carried from person to person? What provision is made for the perpetuation of these highly evolved parasitic organisms, which, in the case of the human host alone, have a life cycle adapted only to the particular individual in whose blood they thrive? Experiment has thrown some light, in that it was found possible to inoculate healthy men by subcutaneous or intravenous injections of blood containing malarial organisms, so as to produce the fever characteristic of the particular type of hematozoa present in the infected man. All other attempts to cause infection through air, water, and by contagion were fruitless; and,

of course, the method of direct inoculation is not Nature's method. It was at this stage of the problem that Smith's observation on the role of the cattle-tick in Texas fever, and of Ross on the gray mosquito in bird malaria, directed the attention of students of human malaria into similar channels, with the result that to-day we have overwhelming evidence to show that *the mosquito is the chief agent, if not the only one, in transmitting malaria from one person to another.* Of the interesting and elaborate investigations—many of which are still in progress—which led to this result, it is impossible here to speak in detail; but the results are widely accepted as unquestionably authoritative. And we may now speak with confidence of the other stage or cycle in the evolution of the malarial parasites: that passed in their intermediate host, the mosquito. Recorded observations have furnished many details with reference to the estivo-autumnal hematozoon, and the same phenomena have been observed, with certain minor modifications, in the tertian and quartan parasites. We shall consider only those best known and least open to modification, relating to the estivo-autumnal parasite.

The second cycle in the life history of the estivo-autumnal hematozoon is in a general way as follows: A mosquito of the proper species and sex stings a human being whose blood contains malarial crescents—these being the so-called sterile forms not capable of producing auto-infection, or, in other words, incapable of asexual reproduction—abstracting some of the blood, which finds its way into the stomach (mid-intestine) of the mosquito. Here the crescents are set free and become ovoid; some flagellate; others do not, but, remaining quiescent, are fertilized by the flagella.¹ Here again we have the biologic equivalents—the *microgametocyte* producing the *microgametes*, which in turn fertilize the *macrogamete*; but, contrary to what is observed in artificial condition, the life history of the fertilized or gamic cell may now be followed. What happens here is much the same as noted in proteosoma when ingested by the gray mosquito. The fecundated or gamic cell traverses the epithelium of the mid-intestine, to find its way between the muscle-fibers or in the adipose tissue adjoining the muscular layer; here it comes to rest, and, for a period estimated at about eight days for the hematozoon of estivo-autumnal malaria, under favorable conditions of temperature, undergoes a striking transformation. The pigmented body increases rapidly in size, becomes enveloped in a capsule, and projects more

¹ At this writing, the actual phenomenon of fertilization has not been witnessed in the stomach of the malarial mosquitoes (genus *Anopheles*); but there is every reason for believing that this is where it takes place. It may seem contradictory to find that flagellation and fertilization can take place in freshly removed malarial blood; that is, *in vitro*, as MacCallum and others have seen in the case of halteridium and the estivo-autumnal parasite; from which some have too hastily concluded that the same operation takes place in the circulating blood of the principal host, although it has long been known that flagellated organisms only appear in extravasated blood, and not until some little time has elapsed. In all probability no spermatogenesis and no fertilization of hematozoan forms predestined for sexual purposes take place in the circulating blood of the principal host; but in the operation of removing the blood for microscopic examination some physical change is induced (some restraining influence abolished?), permitting the extrusion of the flagella, which then go on to perform their function of fertilization. Something of the same kind, but probably more perfectly adapted to the purpose, must happen when the blood is sucked into the proboscis and stomach of the mosquito. Probably because of the less perfect conditions afforded by our laboratory methods of examination, the act of flagellation is somewhat abnormal, accounting for the irregular and often degenerative phenomena here witnessed. If it has not already been done, a method of examination in which the sucking apparatus of the mosquito, or its juices (like those of the mid-intestine), are employed as a medium, will perhaps be found to yield results more like those taking place naturally.

and more into the celoma or body-cavity (pleuroperitoneal cavity in higher animals). Its protoplasm becomes striated and finally breaks up into innumerable filaments, each of which is provided with a speck of chromatin from the nucleus of the mother-cell (*sporocyst*). The products of this much-repeated nuclear and cellular division, the nucleated filaments, are embryonic hematozoa—that is, *sporozoites*. They are slender filaments, usually slightly curved, in the center of which are a few particles of chromatin. The capsule of the sporocyst breaks, and the sporozoites swarm into the body-cavity of the mosquito, many of them finding their way to the tubules, acini, or lumens of the salivary poison-gland of the insect, from which point of

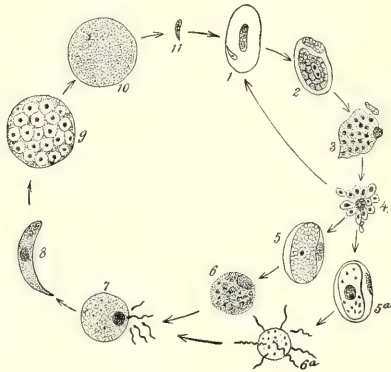


FIG. 101.—Developmental cycle of proteosoma (diagrammatic) (after Schaudinn): 1. Sporozoite (merozoite), after penetration into a red corpuscle. 2. Adult schizont. 3. Nuclear multiplication preparatory to schizogony (asexual propagation). 4. Formation of merozoites (schizogony). 5 and 5a. Immature sexual elements (5, macrogamete; 5a, microgametocyte). 6 and 6a. Mature sexual individuals (6, macrogamete after expulsion of the karyosome; 6a, microgametocyte in stage of microgamete-formation). 7. Copulation. 8. Ookinete—the elongated motile body resulting from copulation. 9. Formation of sporoblasts in the oocyst. 10. Sporozoite-formation. 11. Sporozoite.

vantage they are readily inoculated into the human being with the secretion of the gland, when the mosquito again stings. Fig. 101, from Schaudinn, gives a good representation of the present views concerning the developmental cycle of proteosoma, and also represents that of the *Plasmodium* malarie.

Malarial Mosquitoes and the Mode of Infection.—The process sketched above has been fully verified by experiments carried on in the laboratory and at the bedside. Estivo-autumnal malaria has been induced in human beings by causing them to be bitten by malarial mosquitoes which had sucked from infected patients the blood containing the *gametes* or crescents, and, after the interval previously determined as requisite for the dissemination of the sporozoites, used as agents of infection. These experiments on man, obviously few in number, are only the repetition of those successfully carried out by observers in numerous instances with the proteosoma of birds.

In the course of these experiments, however, it has been determined that only certain kinds of mosquitoes serve as the intermediary host for the plas-

modia of human malaria; in fact, at present only members of the genus *Anopheles* have been found to act as agents of infection. Probably all species of this genus are capable of transmitting malaria, although actual observations have thus far been made in Europe on only three species: *A. claviger* (*maculipennis*) [equivalent to *A. quadrimaculata* of the United States], *A. bifurcatus*, and *A. pictus*. None of the more common mosquito genus *Culex* has been found to harbor the malarial organism of man. Zoologic study upon these malarial mosquitoes has determined that only the females obtain nourishment by sucking human blood—that is to say, only the females of anopheles carry malaria; and the appearance of malaria in certain districts has been found to correspond perfectly with the predatory habits of these mosquitoes. Nothing positive has been discovered as to the possibility of the malarial sporozoites finding their way into the eggs of anopheles, and from here to the larvæ, though such a process is not an improbability. The data concerning the epidemiology of malaria, as now explained by the distribution and life habits of the malarial mosquitoes, cannot here be detailed; but before dismissing this important new phase of parasitologic investigation, we must refer to the positive results in the crucial tests of the malarial mosquito theory now in progress in the deadly Roman Campagna, where two observers are living in perfect health in the midst of

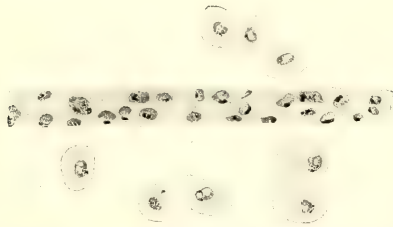


FIG. 102.—Brain-capillary with pigmented tertian parasites (after Celli) (Mannaberg).

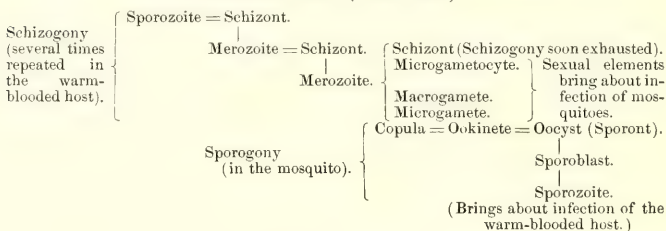
this notoriously malarious swamp, with only the mechanic protection against the ravages of mosquitoes afforded by a mosquito-proof dwelling.

Morbid Effects.—The chief effect of simple malarial infection is the destruction of red blood-cells and the setting free of blood-pigment, which is taken up by the cells of certain organs, especially the spleen. The sterile parasitic forms, or gametes, which do not find exit, also disintegrate, not infrequently falling a prey to phagocytes, particularly those of leukocytic origin. The task of ridding the body of pigment and of defunct parasites falls to the phagocytes; and this is why phagocytosis, both by the leukocytes and fixed-tissue cells, is so prominent a phenomenon in malarial infections.

In the so-called pernicious agues and in the cachexia of chronic malaria, more pronounced gross and microscopic lesions are found. The spleen is enlarged, sometimes soft and pultaceous, due to intense engorgement of the blood-vessels of the pulp; again firm, especially in cases where the reticulum is increased in amount and the vessels of the pulp dilated. A diffuse deposit of pigment is evident. The liver also is swollen, and microscopically shows diffuse pigment and a plugging of many of the finer blood-vessels with

phagocytes. Thrombosis may be the result, and may, according to Barker, bring about the focal necroses at times seen in the liver. The brain may show either microscopic or macroscopic pigmentation; and in the cerebral capillaries the blood is seen to be extensively infected with parasites and to harbor numerous phagocytes. These vessels are often occluded by the infected red cells and phagocytes, producing a deleterious effect on the vessel-wall, by which the cerebral focal hemorrhages of pernicious malaria are produced. Infection of the blood in the vessels of the gastric and intestinal mucosa is also observed at times; and the kidneys frequently suffer parenchymatous degeneration. In pernicious hemoglobinuria this alteration of the kidney is encountered, and the liver also may show diffuse parenchymatous degeneration, its biliary canals being extensively injected with inspissated bile.

SCHEME SHOWING CYCLE OF DEVELOPMENT OF PLASMODIUM IN TABULAR FORM (from Lühe).



PARASITIC INFUSORIA.

Among the free-living forms, the protozoan class Infusoria includes a large number of representatives. Its parasitic members are not so numerous and belong chiefly to the flagellate group. On morphologic grounds the parasitic infusoria may be divided into the subclasses *Flagellata* and *Ciliata*.

Flagellata generally have a pyriform shape, both ends being acuminate; the end put forward in progression is more pointed and is continued into one or more long appendages or flagella. Several organisms belonging in this category are also provided with a so-called undulatory membrane, a peculiar structure extending along the body-wall and showing a rhythmic wave-like motion. This structure, the nature of which was indefinitely understood, is revealed as a red filament in certain flagellata stained by the Romanowsky method, and is continuous with the flagellum, being anchored in the posterior portion of the organism by a round red body. Treated by this method, these flagellata also exhibit a well-defined oval nucleus situated in the parenchyma, usually near the anterior end.

Reproduction takes place by direct binary fission of the mature flagellata. A process of conjugation has also been witnessed, and a difference in the conjugating bodies has suggested a distinction into male and female individuals. In certain species an asexual mode of reproduction has been observed (in *Trypanosoma* of the rat), and here the division of the nucleus, the formation of new flagella from the spheric body anchoring the maternal one, and the division of the cytoplasm have been noted. In some cases a large

plasmodial mass, with numerous nuclei in various stages of indirect division, can be seen before the flagellata separate and leave the colony.

Parasitic flagellata have been encountered in the body-cavities principally, although one genus infests the blood of vertebrate animals. Although their classification is imperfect, several genera have so far been distinguished.

The genus **Plagiomonas** of Grassi, or **Cystomonas** of Blanchard, is characterized by two anterior flagella and a long, tapering, flagella-like posterior end. Here one human parasitic species is included, *Plagiomonas urinaria*, found by Künstler in the freshly passed urine of a patient suffering with chronic purulent cystitis.

The genus **Trichomonas** (Donné) includes flagellata with three or four flagella, often united, and with an undulatory membrane. The posterior portion is decidedly acuminate, but not prolonged into flagella. It includes several parasitic species, some having long been known. One of these, *Trichomonas vaginalis* (Fig. 103), is variable in shape, spindle-formed, or irregular. Its anterior end is generally provided with four flagella, united at their base. A spiral undulatory membrane passes over its body. Near the base of the flagella the organism has a mouth and short esophageal pouch, and in its parenchyma a nucleus is situated. As the name indicates, the habitat of this organism is the vaginal secretions; and since it appears in apparently healthy women, it is questionable whether it can excite the vaginitis which has sometimes been ascribed to it. In a case of cystitis in which no other exciting factor could be determined, Dock found an organism apparently identical with *T. vaginalis*, and he thought the flagellate to be pathogenic. *Trichomonas* (*Cercomonas*) *hominis* resembles the foregoing organism, except that its undulatory membrane is hardly visible and it has several vacuoles, none of them contractile. It has been repeatedly encountered in the stools of human beings under a variety of conditions, as in



FIG. 103.—*Trichomonas vaginalis* (after Kolliker and Scanzoni).



FIG. 104.—*Trichomonas intestinalis* (after Zenker).

cholera, typhoid fever, chronic enteritis, and acute or subacute diarrheal affections. Epstein records the presence of this parasite in twenty-six children suffering with diarrhea. The pathologic significance of the organism is, however, not known. Grassi claimed negative results in attempting to infect dogs with feces containing the *Trichomonas*. But Epstein is positive that in the case of six children in one family, who simultaneously developed diarrhea, the trichomonads, present in their stools and absent in a nursing infant of the same family, were the etiologic agents. On the other hand, Schuberg and others have found flagellata resembling this species, and

also amebæ, in healthy persons after the exhibition of saline cathartics ; so that in all probability these protozoa usually exist in the intestines of man in a state of commensalism. Quinke has described a number of cases, some fatal, of so-called *protozoan enteritis*, in which both flagellate and non-flagellate organisms were found. He claims to have definitely identified, as provocative of diarrheal and sometimes dysenteric symptoms, *Trichomonas intestinalis* (Fig. 104), *Cercomonas hominis*, *Megastoma entericum*, *Coccidia*, *Balantidium coli*, as well as *Amœba coli*.

Another flagellate genus is **Lamblia** of Blanchard, the principal parasitic species of which is *Lamblia intestinalis* (*Megastoma entericum* of Grassi). This organism—which, like the other flagellata, is pyriform—is distinguished by the possession of an adhesion-apparatus in the form of a concavity near its larger end, provided with a contractile elevated ridge or lip, and by the presence of four pairs of flagella, two pairs of which arise from the lowermost or posterior portion of the adhesion-excavation, one from its uppermost or anterior portion, and one from the acuminate posterior extremity of the



FIG. 105.—Infusoria found in the stools in protozoan enteritis (after Salomon).

organism. The organism is endowed with a dense cuticle, the protoplasm is finely granular, and a dumbbell-shaped nucleus lies at the bottom of the excavation. By virtue of its adhesion-apparatus, the organism attaches itself to the epithelial cells of the intestine. It has been found in various diarrheal affections, but its pathogenic effect is questionable ; from its frequent presence in the stools of healthy individuals, it is generally regarded as a harmless messmate. Grassi has described an encysted form of the organism, the oval cysts being found in the stools.

Flagellata have also been found in the sputum in cases of pulmonary gangrene, and in the gangrenous pulmonary parenchyma at autopsy. These observations have been several times confirmed from different sources, and the organisms were also found in the pleural exudate in a case of pulmonary gangrene, and once in pleural effusion where no such disease of the lungs existed.

Another group of flagellata, sometimes classed as a separate genus or family, is **Trypanosoma**, comprising organisms of an elongated spindle-

shaped outline, with a single flagellum and a well-defined active undulatory membrane. This is the class of flagellata in which the Romanowsky stain shows the continuity of the flagellum and the undulatory membrane referred to above. The type of this group is *Herpetomonas Lewisii*, discovered in the blood of the rat by Osler, and recently made the subject of interesting studies by Rabinowitsch and Kempner, who have concluded that the active agent in carrying this organism from rat to rat is a flea infesting these rodents. Direct infection by means of these fleas could not be produced in the laboratory; but, by causing these insects to ingest the blood of a rat infected with this trypanosoma, other rats could be infected by intraperitoneal injections of an emulsion made of the crushed fleas in sterile fluids.

Trypanosoma sanguinis is still another representative of this class of flagellata, appearing in the blood of amphibia, fishes, and birds, although apparently of no pathogenic significance.

Somewhat in keeping with the results obtained in the case of the trypanosoma of rats are the recent investigations upon two peculiar diseases of horses, mules, and camels in India, known as the *Surra disease*, and *Nagana* or the *Tsetse-fly disease*, which also affects cattle and dogs. Evans discovered a flagellate organism in the blood of animals affected with Surra disease, and Bruce found one in the tsetse-fly disease which he thought to be the specific causative agent. Koch confirmed these conclusions and believes that the two affections, as well as the flagellata, are identical. Injections of infected blood suffice to transfer nagana, and Bruce believes that the tsetse fly is the intermediate carrier of the infecting flagellata, a view concurred in by Plimmer and Rose Bradford.

Among the **Ciliata**, which include a number of highly differentiated protozoan organisms familiar to zoologists, two representatives only need be mentioned: *Balantidium coli* (Fig. 106) and *Vorticella*. The first organism, which has a close morphologic resemblance to the familiar slipper animalcule of standing water, has often been encountered in normal human feces, and especially in that of diarrheal disorders. Its pathogenic action is questionable. *Vorticella*, illustrated by the bell animalcule of fresh water, has been found by Lindner in the human being under a variety of conditions, as in the stools of a typhoid patient, in the urine, in the nasal secretion, and in an eczema-like disease of the skin. It is well known that this organism, generally anchored by a contractile stalk, can free itself and swim about in fluids; and in this state it might find access to the human body. Lindner's observations, however, need confirmation, since they assign much importance to these vorticellæ as pathogenic organisms.

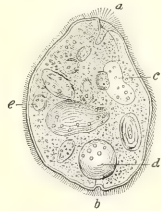


FIG. 106.—*Balantidium coli*
(after Malmsten).

ANIMAL PARASITES.

PARASITISM IN GENERAL.

THE dominant condition in parasitism, says Davaine, is "the subordination of one individual to another individual which is never of its own family." The condition of parasitism has a wide distribution, both in the vegetable and animal kingdoms; and man, in common with other representatives of the latter, harbors many forms of parasitic animal life.

Most parasites require a change of abode before arriving at maturity, therefore the animal which shelters the parasite during its immature existence is called the "intermediate" host, as distinguished from the "definitive" host in which development is completed. A few species require no intermediate host. Leuckart divides parasites into "stationary," those whose stay in the one host may be for their life, and "periodic," those whose stay is only a part of their cycle of life. Another division frequently used is that into external (ectoparasites or ectozoa), and internal (entoparasites or entozoa). The former class is made up principally of insects, the latter of worms.

The changes produced in the host by the parasite vary greatly in their consequences. In the case of tapeworms, for instance, no great amount of nourishment is abstracted from the body. Heller states that the average weight of eight specimens of *Tænia solium* was 10 grams, the maximum 19.9, and the minimum 5.1. The average weight of *T. saginata* was 42 grams, the maximum 64, the minimum 31. Since a tapeworm requires at least eight weeks to become mature, the loss could not exceed 64 grams, which would be quite insignificant. It is entirely different with the species living on the blood, for here the continued drain entails serious and even fatal consequences. However, even in these, it is only their presence in large numbers that renders them formidable (*Ankylostoma*). It is needless to say that, if parasitism in general were very dangerous, the condition would ultimately cease, owing to the death of all the hosts.

Some worms, especially the Nematodes, are intensely irritating when handled. Miram, while studying the round worm, was attacked by sneezing, swelling of the lacrimal passages, itching and swelling of the fingers. Cobbold

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Davaine, C., et Laboulbène, H.: Article "Parasites, Parasitisme," in *Dict. Encyclopédique des Sciences Médicales*, 2me series, vol. xxi., p. 66.

Heller, Arnold: Article "Intestinal Parasites," in Ziemssen's *Handbook*, vol. vii., p. 669, New York, 1876.

Leuckart, R.: *Die menschlichen Parasiten*, vol. i. Translated by W. E. Hoyle, Philadelphia, 1886.

Manson, Patrick: Article "Worms," in Allbutt's *System of Medicine*, vol. iii., p. 1006, New York, 1897.

and Bastian have noticed the same effects even in alcoholic specimens, the latter having catarrhal symptoms for six weeks. Lussana and other authors believe the pathologic symptoms produced by *Ankylostoma* are due to some poison given off from the worms themselves. The broad tapeworm (*Bothriocephalus*) is another species which seems to secrete some poisonous material.

Concerning the effects on the parasite, it may be said that many of the organs necessary for its life in a free state have degenerated or entirely disappeared on account of the change in environment. The reproductive organs, on the contrary, have become more prominent, and the body of many parasites is chiefly composed of these organs. The ova are produced in almost incredible quantities, probably owing to the vicissitudes to which they are liable. Leuckart points out that during an average life of a tapeworm it will produce about 1500 segments, each containing some 53,000 ova, or a total of say 85,000,000. Now, since the number of tapeworms remains about the same, only one of all these millions reaches maturity. The probability against a tapeworm egg ever becoming a mature animal is as 85,000,000 to 1.

The adult parasites are usually found in those cavities communicating with the exterior; the immature forms are scattered through the body and do not exhibit such marked preferences for certain locations as do the adults.

Bunge kept worms in a medium deprived of oxygen, in which they remained alive from four to seven days, exhibiting great activity. He suggests that parasitic worms have descended from anaerobic free-living forms, whose ancestors again were aerobic. As corroborating this theory, Bunge points out that nematode ova will not develop without oxygen; hence the young worms are not parasitic at first, but as a rule live free.

Individuals at all ages are liable to be attacked by internal parasites. Some species are found chiefly in children and young persons, others are met with at all periods of life to extreme old age. The female sex is more exposed to helminthiasis on account of active participation in culinary affairs, about 60 or 70 per cent. to 30 or 35 per cent. of males. Occupation also has considerable influence. (Of 173 patients of Wawruch, 39 were cooks, 26 servant-girls, and 13 innkeepers or butchers.) The season of the year is of some importance. The tapeworms seem more abundant in the winter on account of the great use of a flesh diet then; *Oxyurus* in the spring, *Ascaris* in the spring and fall, etc. Persons living in the country are more exposed to parasites than town dwellers, both on account of the more favorable opportunities for infection and the greater use of unfiltered water (57.31 per cent. country children, 16.66 per cent. city children, Langer).

In man, as in other animals, the vast majority of parasites belong to the subkingdoms Vermes and Arthropoda.

VERMES (Worms).

The parasitic worms belong to two classes—the flat worms and the round worms.

Plathelminthes.—Plathelminthes or flat worms have a flattened body, with the organs embedded in the parenchyma; there is no body-cavity. Of the three families comprising them, only two are parasitic.

Trematoda (Flukes).—The Trematodes or Flukes are worms with a soft, flattened body, not segmented, and ovate or lanceolate in shape. The body is smooth or covered with small spines directed backward, and provided with one or more suckers, of which the posterior one only is used for adhering to the body of the host (Fig. 107). Most of the species are hermaphrodite; the ova develop into ciliated free-swimming larvæ which require one or more intermediate hosts before arriving at maturity in the final host. It is an interesting fact that species of Trematoda which are capable of living in the stomach of one host are, as a rule, quickly digested when placed in the stomach of a strange host. This has led several observers, notably Max Braun, to conclude that the cutaneous secretion only protects each species against the juices of its proper host.



FIG. 107.—*Fasciola hepatica*, natural size, viewed from ventral surface.

Fasciola hepatica (*Distoma hepaticum*), the liver fluke, is a frequent parasite in sheep and cattle, occupying, as its name indicates, the bile-passages. In man it is found occasionally in the gall-bladder, bile-ducts, blood-vessels, and subcutaneous tissues; about two dozen cases have been reported to the present time (Fig. 107). This species is from 15 to 35 mm. in length and from 4 to 15 mm. in width, white, with body pointed at each end, and two suckers—the oral, into which the pharynx opens, and a larger one close behind on the ventral surface. The external surface is covered with spines. The eggs are yellowish brown, oval, quite large, measuring 0.13 to 0.15 by 0.07 to 0.09 mm., and furnished with a lid.



FIG. 108.—Papillary thickening of the mucous membrane of the bladder, showing distoma eggs *in situ* (Mosler and Peiper).

In sheep this worm gives rise to the "rot," which is exceedingly fatal in some years. In man the bile-passages may be enlarged, their walls thickened or obstructed. The liver may also be enlarged, and there may be hepatic pain, jaundice, vomiting, diarrhea, and ascites. In some cases no pathologic effects seem to have ensued. If only one parasite is present, its location may have some influence—*e. g.*, if it is located in the common bile-duct or the hepatic duct. Owing to the usual location of the worm in the bile-passages, the only means of diagnosis is the microscopic examination of the feces for eggs. The egg resembles that of *Bothriocephalus latus* (q. v.), from which it may be distinguished by its much larger size. Infection

occurs through ingestion of water containing the embryos or of food-plants containing the encysted larvæ.

Dicrocoelium lanceolatum (*Distoma lanceolatum*), the small liver fluke, is nearly as widespread in sheep and cattle as the former and is frequently associated with it. The body is 8 to 10 mm. in length by 2 to 2.5 mm. in width, white, thin, and broader posteriorly. The two suckers are farther

apart than in the preceding, and the genital pore is found between them. The eggs are black, 0.04 to 0.045 by 0.022 to 0.08 mm., and are also provided with a lid. It has been discovered five times in man, in one case associated with the former species. The lesions caused are the same, but it appears to inflict less damage on account of its much smaller size.

Opisthorchis felineus (*Distomum sibiricum*) is found in the bile-passages of the domestic cat. This fluke is 10 to 13 mm. in length by 2 to 2.5 mm. in breadth; the eggs are oval, 0.026 to 0.030 by 0.010 to 0.015 mm. It has been found in the cat in various parts of Europe, and once in this country by Ward. In parts of Siberia it is one of the commonest parasites of the liver, about Tomsk occurring in 6.45 per cent. of the necropsies (Winogradoff). According to this author, the lesions it may cause are atrophy of the liver, icterus, ascites, and less frequently hypertrophy of the liver and suppurative cholangitis. Several hundred individuals are sometimes found in a single cadaver.

Opisthorchis conjunctus (*Distoma conjunctum*) is 10 to 12 mm. in length by 2.5 mm. in width; the anterior sucker is larger than the posterior and in close proximity to it. The surface is covered with small spines, by which it may be distinguished from the next species. The eggs are oval, 0.034 by 0.020 mm., and furnished with a lid. It has twice been found in man in India. Both cases presented thickening and dilatation of the bile-passages, in which the distomes were very abundant.

Opisthorchis sinensis (*Distoma sinense*) is 10 to 15 mm. in length by 2 to 4 mm. in width, with a narrow, translucent, colorless or slightly reddish body and a smooth surface; the posterior sucker is smaller and situated far back. The eggs are oval, blackish, 0.028 to 0.030 by 0.016 to 0.017 mm., and are provided with a lid. This species resembles *D. lanceolatum* and *O. conjunctus*. In *O. sinensis* the posterior sucker is smaller, in *D. lanceolatum* the anterior is the smaller. In *O. sinensis* the cuticle is smooth, and in *O. conjunctus* spiny. It has been found in India, Tonkin, China, Formosa, Corea, Japan, and once in New York City. It has not yet been found in Europeans. In low-lying parts of Japan, according to Bälz, fully 20 per cent. of the population is affected. The liver and spleen become enlarged, there are chronic diarrhea, recurrent jaundice, and later ascites. Nutrition is not affected till late, for Bälz saw patients working in the fields who had been suffering for six years.

Opisthorchis Buski (*Distoma crassum*), the largest fluke known to attack man, is 4 to 8.5 cm. in length by 1.7 to 2 cm. in width; the body is elongate, narrower in front, very thick and smooth; the suckers are close together, the posterior being the larger. The eggs are 0.125 by 0.075 mm., with a lid. It inhabits the small intestine, and has been found in India, Assam, Straits Settlements, China, and in an East Indian coolie in British Guiana. In parts of India it is very frequent, and was found by Dobson in 1 per cent. of the coolies. It produces symptoms of intestinal irritation, indigestion, diarrhea, but no dysentery, although clots of blood may be in the stools.

Mesogonimus heterophyes (*Distoma heterophyes*) is 1.5 to 2 mm. in length by 0.7 to 1 mm. in width. The body is an elongate oval, with the posterior end rounded off, reddish in color from the contained eggs, and the front half is covered with spines; the posterior sucker is unusually long and situated about the middle of the body. The eggs are 0.025 by 0.015 mm., and reddish in color. It is found free by hundreds in the small intestine;

but, unlike the species mentioned hitherto, its intestine contains no blood and it is presumed to be harmless. Up to the present time it has been met with only in Cairo, Egypt.

Mesogonimus Westermanni (*Distoma Ringeri*, *D. pulmonale*) is the cause of "endemic hemoptysis." It is 10 to 16 mm. in length by 5 to 8 mm. in width, reddish brown, covered with spines, and in transverse section is nearly circular. The eggs are 0.08 by 0.05 mm., reddish brown, with a thin shell and lid. It is extremely frequent in Formosa, at least 15 per cent. of the population being affected (Manson), and is equally frequent in Japan, where Bälz found over 100 cases from all parts of the country; it also occurs in Corea. In this country it has been found by Ward¹ in a cat at Ann Arbor, Mich., and by Kellicott in a dog at Columbus, Ohio. The usual site is the lung, the parasite being found in cavities in the periphery of the organ, which communicate with the bronchi by small openings and contain mucopurulent fluid more or less tinged with blood, containing flukes, eggs, and Charcot-Leyden crystals. It is also found in the liver and peritoneum, and not infrequently emboli of the ova become lodged in the brain, where they give rise to cortical epilepsy. The patients have a constant cough, with expectoration of sputum colored like that in pneumonia, due to the numerous eggs. The cavities open into the blood-vessels, from time to time causing attacks of hemoptysis.

Schistosomum hæmatobium (*Bilharzia hæmatobia*, *Distoma hæmatobium*).

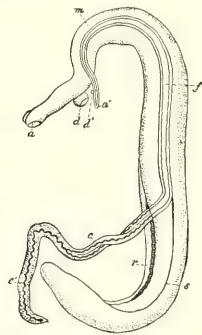


FIG. 109.—Male and female *Schistosomum hæmatobium* in the act of copulation. The male (*m*) encloses in its ventral groove (*v*) a female (*f*), whose two extremities are free and pendent; *a*, cupped mouth of the male; *a'*, cupped mouth of the female; *c*, intestinal branches; *c'*, single cul-de-sac proceeding from their junction in the posterior portion; *d*, abdominal cup of the male; *d'*, abdominal cup of the female; *s*, base of canal (after Bilharz).

—In this species, the cause of "Egyptian hematuria" or bilharziosis, the sexes are separate (Fig. 109). The male is 11 to 14 mm. in length by 1 mm. in width, whitish, the sides of the body folded over to form the gynecophoric canal in which part of the female is contained *in coitu*. The female is 15 to 20 mm. in length, very thin and darker in color. The eggs are elongated, 0.12 by 0.04 mm., with a spine either at one pole or placed laterally. It is found in Egypt, Abyssinia, Arabia, Mesopotamia, and South Africa; occasionally elsewhere, *e. g.*, in a donkey-boy from Egypt at the World's Fair in Chicago (Hillmantel).² It is very frequent in Egypt, and was found by Griesinger 117 times in 363 necropsies, and by Sonzino 30 times in 54 necropsies. It attacks either the genito-urinary system, producing vesical symptoms, or the rectum, causing dysenteric symptoms. The fluke is found in the portal vein, and its branches in large numbers (as many as 300 by Kartulis) in the renal veins and in the venous plexuses about the bladder and rectum (uterine, vesical, and hemorrhoidal). Its presence causes blocking of the vessels by ova, and leads to catarrhal inflammation with small hemorrhages in the mucous membrane of the bladder and ureter. In cases of long standing there is proliferation of the connective tissue, and the surface of the mucous

¹ Ward, *Med. News*, p. 236, March 2, 1895.

² *Chicago Med. Rec.*, p. 230, Oct., 1893.

membrane is studded with small papillæ made up of proliferated cells encrusted with urinary salts (Fig. 108). The eggs are found in the tissues and the mucus covering the surface. Similar changes take place in the rectum when it is involved, and polypoid growths occasionally develop. Primary infection of the vagina is rare, but when it occurs the same changes are found. The principal symptom of bilharziosis is hematuria, varying in amount from a few drops to a large quantity. The characteristic ova are found free or else entangled in clots of blood and mucus in the urine when it is allowed to settle. Lortet estimates that from 3000 to 4000 eggs are voided daily with the urine.

Amphistomum hominis is 5 to 8 mm. in length by 3 to 4 mm. in width; the posterior sucker is very large and much wider than the remainder of the animal; the genital pore is situated between it and the oral sucker. It is found in India and Assam, occurring by the hundreds in the large intestine (cecum, appendix, and ascending colon). It was originally found in two cases of Asiatic cholera, and its importance is problematic.

Cestoda (*Tapeworms*).—The tapeworms are ribbon-like animals made up of segments and varying from a few millimeters to several meters in length. They are exclusively parasitic, and as a result have become greatly modified in structure; there is no trace of mouth or any other part of the alimentary canal, and they are nourished by the partly digested food of their host, which they absorb through the skin. Firm adhesion to the host's intestine is necessary in order to avoid the loosening action of peristalsis as the food passes along, which is provided for in various ways.

The question as to whether a tapeworm is a single animal or a colony of animals is still in dispute. According to the older view, a tapeworm is a colony of two generations—the head and neck produced by the larva, and the joints or *proglottides* produced by segmentation from the head. More recently the view that there is but a single animal has been advanced. The "ripe" proglottides are expelled with the feces or they escape spontaneously (Fig. 111). They are literally stuffed with eggs, which are liberated either by decomposition of the proglottides or by some animal swallowing the latter. The embryo has three pairs of hooks (hexacanth), and by means of these it bores through the alimentary canal of its host, having previously lost its covering, which was dissolved by the gastric juice. Once through the intestine, it makes its way to the tissue in which it is apt to become encysted—in the muscles, connective tissue, liver, or other viscus—and awaits here a transfer to the final host. Man harbors most tapeworms, both in the adult and larval stages; the *Tænia echinococcus* is found only in the larval form in human subjects.

Tænia saginata (*T. mediocanellata*), the unarmed or beef tapeworm, has an average length of 8 to 10 meters. The head is 1.5 by 2 mm., large enough to be seen by the naked eye and frequently colored dark gray or black. The top is plane or even slightly concave, and has four powerful sucking disks, but no hooks. A rather long neck succeeds the head, and then comes the body proper, consisting of 1200 or more segments (Fig. 111). The first segments have no traces of sexual organs; the testes are the first to appear, farther along are the female organs, and finally the ova in the segments farthest from the head. The six-hundredth segment would be about the first to show any sign of sexual organs, the ova appearing about the one-thousandth segment, and the last 100 or 200 are ripe segments.

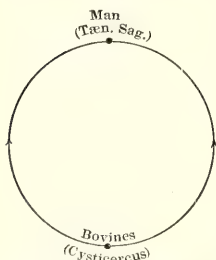
The sexually mature segments are greater in length than in breadth; the largest segments are not at the extreme end of the chain, for these have been partly emptied of eggs.

The head is fixed to the mucous membrane of the intestine close to the pylorus, and, while not armed, is harder to expel than the armed species.

Usually only a single worm is present, although as many as twenty-five have been found. (Of 2686 patients in the French naval hospitals, 2341 or 89 per cent. had only one tapeworm—Berenger-Feraud.) They are seen in patients of all ages, from nurslings to persons of over eighty years, most of the patients being between twenty and fifty years of age.

The larval form is the *Cysticercus bovis*, which is found in the connective tissue of the striped muscles and occasionally in the viscera of cattle; hence man is infested by eating raw or partly cooked beef (Fig. 110). The duration of life of the cysticerci is not accurately known, but they probably live for several months or even years.

FIG. 110.—Life cycle of *Tænia saginata* (after Bollinger).



In the ox the cysts are round, small, less than 1 cm. in length, and few in number. They are not found in man, although two or three doubtful cases are reported. After the cyst is swallowed, two or three months elapse before the segments appear. From Perroncito's experiments, it is probable that the worm grows to about 72 mm. and produces 13 to 14 segments daily.

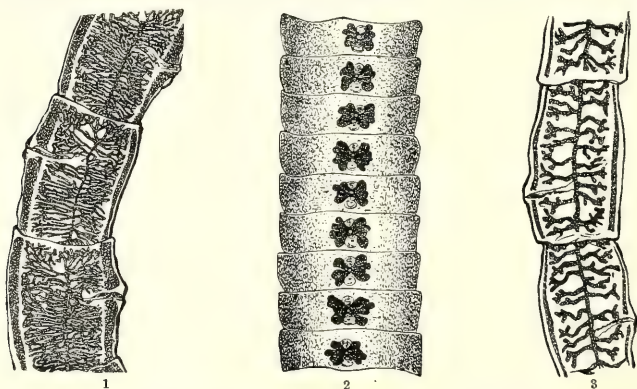


FIG. 111.—Segments of (1) *Tænia saginata*, (2) *Bothriocephalus latus*, and (3) *Tænia solium*, showing the arrangement of the uterus.

The beef tapeworm is cosmopolitan and is found wherever beef is eaten, though the percentage of affected individuals varies greatly. Thus it is very common in Eastern Europe, India, and Abyssinia, so much so in the latter country that each adult native is supposed to harbor one or more individuals; in Western Europe and the United States it is less common.

The life of the worm may continue for many years with daily formation of segments. The latter escape singly, and, owing to their well-developed musculature, are able to crawl about the patient's bed, his clothes, or even the walls of the room.

Tænia solium, the armed or pork tapeworm, is a comparatively short worm of 2 or 3.5 meters, rarely 7 or 8 meters, in length. The head is rounded, much smaller than in the preceding, 0.5 to 0.7 mm. in diameter, and provided with a retractile proboscis or rostellum, occasionally colored gray or black. About the circumference of this rostellum are two circles of small hooks, the total number varying from 26 to 32; below the circle of hooks are four sucking disks. The neck is filiform; the body is composed of 850 to 900 segments, which when mature measure from 9 to 10 by from 4 to 6 mm. The sexual organs begin to appear about the three-hundredth segment, and, while the last 80 or 100 segments only are ripe, they make up one-third of the total length. Several segments are voided together instead of singly as in *T. saginata*; they are also not so mobile as those of the latter. The worm is found in the small intestine, adhering to the duodenum or jejunum and extending down toward the ileocecal valve.

The pork tapeworm is also cosmopolitan, though it is becoming less frequent since the discovery of the *Trichina spiralis* and the greater care taken in cooking pork. It is especially rare in the United States. According to Blanchard, for every 1000 specimens of *Tænia saginata* met with in Paris, only 21 specimens of *Tænia solium* occur. The larval form (*Cysticercus cellulosæ*) is found in the pig and various other animals, and, contrary to the usual rule, both larva and adult may develop in man (Fig. 112). Nearly three dozen cases are known of patients harboring *Tænia solium* and *Cysticercus cellulosæ* at the same time.

Cysticercus cellulosæ, the larval form of the armed tapeworm, is the "measles" of pork. It is an oval, translucent vesicle, 8 to 12 mm. in length, found in the connective tissue, especially of the muscles of the tongue, neck, and shoulder, though it may invade nearly every organ. When insufficiently cured or cooked pork is eaten, the larva is set free after solution of the capsule in the gastric juice, the head attaches itself to the mucous membrane, and the adult stage begins. About three months elapse before this is complete.

In man, cysticerci are found in various parts of the body; they are more common in the upper half, and appear to be symmetrically distributed. Large numbers are sometimes found; thus Lancereaux reports a case where over 1000 could be detected subcutaneously. The apparent predilection of

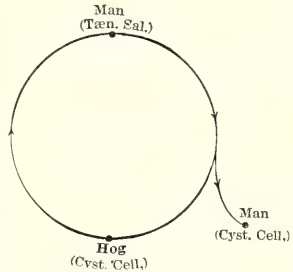


FIG. 112.—Life cycle and intermediate hosts of *Tænia solium* (after Bollinger).

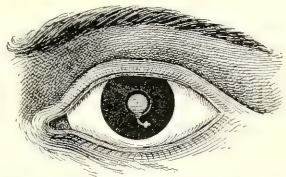


FIG. 113.—*Cysticercus* of the anterior chamber of the eye (Blanchard).

the cysticerci for the brain and the eye is probably explained by the fact that they soon excite symptoms in these locations, while elsewhere they may give rise to none (Figs. 113, 114). In the subcutaneous tissues they form small painless swellings, from the size of a bean to that of a walnut. In the brain they develop into irregular branching forms sometimes called *Cysticercus racemosus*. Cysticerci of the bones and lymph-glands are exceedingly rare, only 2 cases of each being on record. Of 43 cases of cyst of the

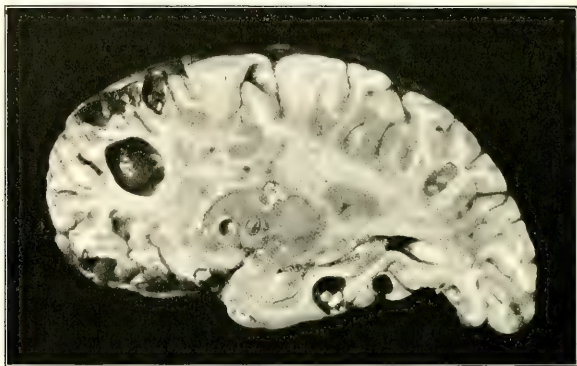


FIG. 114.—*Cysticercus cellulosæ* in the human brain.

cerebral ventricles, 61 per cent. were in the fourth ventricle (Verdun and Iversen¹). In connection with a case of cysticercus of the brain, Diamond² was able to collect only 8 cases of cysticercus in any part of the body reported from America, and none of them probably originated in this country.

Individual segments of *Tænia solium* may be distinguished from those of *Tænia saginata* by the uterus having in the former from 6 to 13 ramifications instead of from 20 to 30 in the latter. If the ramifications are not easily discerned, the segment can be placed in a weak potash solution (1 per cent.) or 20 per cent. acetic acid to clear it up, and then pressed between two microscopic slides and held to the light.

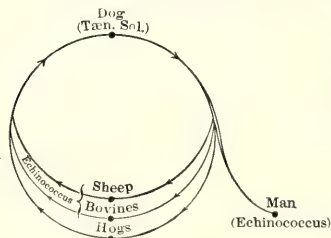


FIG. 115.—Life cycle and intermediate hosts of *Tænia echinococcus* (after Bollinger).

Tænia echinococcus is a small worm, 2.5 or 3.5 mm. in length. The head has a long, prominent rostellum with a double circle of hooks, from 30 to 40 in number; below the hooks are four suckers. The body

is composed of only three or four segments, the last being equal in length to the others combined.

¹ *Arch. de Parasitologie*, i., 344, 1898.

² *Jour. Amer. Med. Association*, p. 1365, June 17, 1899.

While this species has been found in the wolf and jackal, its usual host is the dog, in which it may be found sometimes by thousands in the upper part of the small intestine (Fig. 115). In Iceland, Krabbe found it in 28 per cent. of the dogs; it is also extremely frequent in Australia; elsewhere it appears to be scarce. In man, only the cystic form is found.

The bladder-worms of the two preceding varieties each produce but one head, while those of the present species may produce many. Three varieties of cyst-formation are known:

Echinococcus scolicipariens (*E. veterinorum*, *E. granulatus*).—The embryo, being set free in the stomach, penetrates the mucous membrane and is carried to various organs by the lymph or blood current. When finally lodged, a cyst develops about it—the *hydatid* or *echinococcus* cyst. This is small at first, and the wall is composed of two layers—an outer or cuticular layer which is laminated, and an inner or parenchymatous layer which is granular and contains muscular fibers. Small buds—"brood capsules"—appear in a few weeks, projecting from the inner layer; these become hollow in the center, and from these brood capsules the tapeworm-heads (scolices) grow, some 15 or 20 in number in each capsule (Fig. 116). The scolices project at first, later they are invaginated into the capsule. Sometimes they become

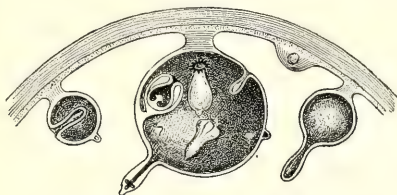


FIG. 116.—Section of *Echinococcus scolicipariens* (Braun).

loose and float about in the interior. The original cyst increases in size by the growth of the capsules, and the cyst-cavity is filled with hydatid fluid. Occasionally the original cyst produces no buds, and it is then known as an "acephalocyst." The *scolicipariens* variety is found chiefly in animals, but also occurs in man.

Echinococcus altricariens (*E. hominis*, *E. hydatidosus*).—In this variety the cyst is much larger, separate "daughter"-cysts are enclosed in the original cyst and are sometimes very numerous, several hundred or a thousand or more. "Granddaughter"-cysts frequently develop in the daughter-cysts, and even a fourth generation may be produced. This variety is found principally in man.

Echinococcus multilocularis is rare, less than 100 cases being known. At first it was thought to be a colloid carcinoma, until its true nature was recognized by Virchow. It consists of a large tumor-like mass, which on section shows numerous small round cavities filled with gelatinous fluid; the center is often broken down into a large cavity, and scolices are rarely found (Fig. 117). The geographical distribution is very peculiar, and only 1 case is known in America. Of 80 cases, 29 occurred in Bavaria, 21 in Switzerland, and 18 in Württemberg. Most of the cases occur in women, and in the right lobe of the liver.

Echinococcus cysts are found in tissues having a good blood-supply, and rarely in unstriped muscle. They are especially frequent in the liver (57 per cent. of all recorded cases); the lung comes next in frequency, then the kidney, spleen, etc. Several organs may be invaded simultaneously. The female sex is more often affected (58 per cent., Neisser). They are found between the ages of ten and fifty.

The pathologic effects of the cyst are due to direct pressure; as it grows, a connective-tissue capsule develops about it, although in cysts growing into

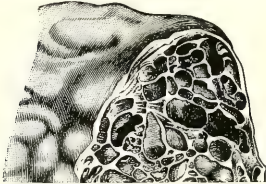


FIG. 117.—*Echinococcus multilocularis* (Luschka).

the body-cavities this may be wanting. They may open on the surface of the body, into various cavities, or into the hollow viscera. Suppuration may occur in the contents, or the parasite may die; the contents of the cyst become caseous and finally calcareous.

Hydatid fluid is colorless, odorless, neutral in reaction, with a specific gravity of from 1006 to 1015.

The solids vary from 1.2 to 1.4 per cent., and consist of sugar and inosit; traces of urea and creatin, sodium chlorid (0.61), and other salts. The pure fluid contains no albumin. It has been known for some time that exploratory or other puncture of a hydatid cyst gives rise to toxic phenomena. Boinet and Chazoulière¹ have found this to be due to a ptomain isolated and studied by them.

If the hydatid tumor be grasped by one hand and percussed with the other, a peculiar vibration will be transmitted, which was supposed by its discoverer, Briangon, to be due to the daughter-cysts striking each other while floating. This is the "hydatid thrill" or fremitus, and it is of much less value in diagnosis than was formerly supposed. It is absent in about half the cases, especially when the cyst is solid or deep-seated, and is found also in ascites



FIG. 118.—*Dipylidium caninum* (Mosler and Peiper).



FIG. 119.—*Hymenolepis murina*, about natural size (Mosler and Peiper).

and ovarian tumors. Bamberger claims it is even more frequent in the latter conditions.

The distribution of hydatid cysts agrees with that of the echinococcus tapeworm. They are very frequent in Iceland and other parts of Europe.

¹ *Rev. de Med.*, p. 845, 1898.

In this country only about 100 cases are on record (Sommer)¹; of these, 33 occurred in New York.

Dipylidium caninum (*Tenia cucumerina*, *T. elliptica*) is a tapeworm from 15 to 35 cm. in length. The head has three or four circles of hooks, from 40 to 60 in number, with four suckers. The neck is filiform; the mature segments, of which there are about 25, are much longer than they are wide (6 to 7 by 2 to 3 mm.), and are of a reddish color from the contained eggs; the genital pore is bilateral (Fig. 118). This species is very common in the dog, and is found in about half the individuals examined. The dog-louse, and occasionally the dog-flea, is the intermediate host. Some two dozen cases have occurred in man, the majority in children.

Hymenolepis murina (*Tenia nana*), the smallest tapeworm infesting man, is from 8 to 15 or 20 mm. in length and from 0.5 to 0.7 mm. in width. The head is from 0.26 to 0.29 mm. in diameter, somewhat



FIG. 120.—*Hymenolepis murina*, showing circle of hooks.

spheric, with a rostellum, a single circle of 24 to 28 hooks, and four powerful sucking disks; the neck is filiform (Fig. 119). The segments are 190 or 200 in number, the last 40 or 50 being mature. The ripe segments are yellowish brown from the contained eggs; the genital pore is on the same side of all the segments. This is a common species in rats and mice, and the former are probably the source of infection. Grassi has shown that in the rat the embryos become encysted in the mucous membrane of the intestine, the cyst ruptures and the animal falls into the intestine, completing its development there. In man it is seen chiefly in children and youths, attaching itself deeply; from 40 to 5000 individuals are found. As rats and mice are met with throughout the world, this species is probably also cosmopolitan. It was discovered in Egypt and is frequent in warm countries, in Siam, Brazil, Buenos Ayres, and in Germany and Italy.

¹ *N. Y. Med. Jour.*, p. 656, Nov. 23, 1895; also, p. 263, Aug. 22, 1896.

Hymenolepis diminuta (*Tenia flavopunctata*).—This is a small tapeworm, 20 to 40 cm. long; its head is very small, cuboidal, with a rostellum and four small suckers, but no hooklets; the neck is filiform. The segments number 1000 or more. The old name was derived from the distended receptaculum seminis, which shines through the anterior segments as a yellow spot; further back the segments become brown from the contained eggs. Nearly every other segment is sterile; the genital pore opens on the same side in all segments. It is a parasite of rodents, especially the house-rat, while the larva is found in insects. It has been seen six times in human beings, always in young children, and the number present was from one to six worms.

Davainea madagascariensis (*Tenia madagascariensis*).—This tapeworm is from 25 to 30 cm. long, the head being round, with a rather large rostellum, and four suckers arranged in two pairs joined to each other; there are no hooklets. The body contains from 500 to 600 segments; the genital pores are on one side, and the eggs are in round masses arranged in transverse rows. Nine cases are on record, all but one in children from Comoro, Mauritius, British Guiana, and Siam.

Bothriocephalus latus, the broad tapeworm, is the longest species infesting man, and measures from 6 to 10 meters or more in length. The head is club-shaped, 2 to 2.5 mm. long by 1 mm. wide; there is no rostellum or hooks, and the sucking disks of the preceding species are replaced by two long and deep grooves, one on each lateral border (Fig. 122). The neck is

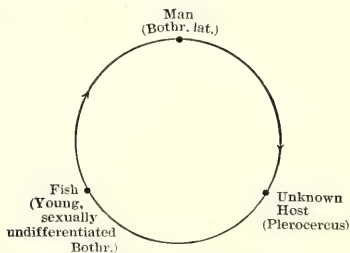


FIG. 121.—Life cycle and intermediate hosts of *Bothriocephalus latus* (after Bollinger).

narrow; the segments, 3000 to 4000 in number, are short and very broad, 10 to 15 by 3 to 4 mm. The genital pores are not on the edge, but on the flat surface in the center of the segment, and are always on the same



FIG. 122.—Head of *Bothriocephalus latus*: a, bothridies; b, neck (Blanchard).

side. The eggs are 0.68 to 0.70 by 0.044 to 0.045 mm., elliptical, brownish, with a lid at one end which becomes more prominent as development advances. They develop in water, slowly; the embryo is ciliated and swims about until it finds a host (Fig. 121).

The broad tapeworm is difficult to expel, and has been known to live in the body for fifteen or more years. But one individual is present, as a rule, though as many as 90 have been voided. About six weeks are required for complete development after the embryo is swallowed. Man may be infested at all ages, and the worm may be found in company with other species of tapeworm. The intermediate host is furnished by various species of fish, especially the pike and burbot (79 of 80 fish examined at Dorpat were found to be infested), and in Japan a salmon (Fig. 123). There are two main centers of infection: (1) The region about the Swiss lakes, including Bavaria and North Italy. (2) The shores of the Baltic—Pomerania, Sweden, Finland, Russia (15 per cent. of inhabitants of St. Petersburg are said to be affected). It occurs sporadically in Belgium, Holland, Japan, and elsewhere.

Bothriocephalus cordatus is a comparatively short tapeworm about 1 meter long, with a heart-shaped head. It is a frequent parasite of the seal, walrus, and dog, in Greenland, and was found there once in a woman.

Bothriocephalus Mansonii (*Ligula Mansonii*) has been found only in man, and in the larval state. The larva is 30 to 35 cm. in length, with transverse striations. It is found in the subperitoneal tissue, in the subcutaneous tissue, under the conjunctiva, and was once expelled through the urethra. It is met with in Japan, China, Australia, and British Guiana.

Krabbea grandis is a long worm, the total length being probably 10 meters or more; the segments are extremely short (0.45 mm.); the head has not yet been found. The sexual organs open into two long grooves on the ventral surface. Discovered by Ijima in a Japanese man, aged 28, who had suffered for years from colic, vertigo, and a progressive anemia which disappeared with the evacuation of the worm. This species may prove to be a parasite of the seal, as the discoverer states that it resembles species of *Bothriocephalus* found in that animal. This view is rendered probable by the known occurrence of *B. cordatus* and *A. maritima* both in man and in the seal.

Anomalies.—*Tænia saginata* and *Bothriocephalus latus* are most frequently malformed. The segments are principally affected; sometimes many are coalesced into one (*Tænia fusa*). Supernumerary segments may be met with, also various anomalies in the number of the genital pores, or even inversion; e. g., in *Bothriocephalus latus* the male organs may be on the edge instead of on the side. Ripe segments are sometimes so full of eggs that they burst, and a ring of tissue is all that is left of the segment (*Tænia fenestrata*) (Fig. 124). The whole worm may be colored dark gray or black by the bile, blood, or medicinal agents (*Tænia nigra*). *Bothriocephalus latus* with a malformed head was described as *B. cristatus*. A prismatic form has been known for over a century. Cattaert¹ proves that it is due to the fusion of two individuals. If the fusion is by edges, a V-shaped form results; if the fusion is more complete, a Y is produced. The head is invariably furnished with six suckers, and the embryos also are malformed.

Symptoms of Tapeworm.—In many cases none are appreciable, in other instances various nervous and digestive disturbances result. Probably the



FIG. 123.—Plerocircoid of *Bothriocephalus latus*: a, with head projected; b, with head retracted (Braun).

¹ *Arch. de Par.*, ii., p. 153, 1899.

psychic effect has some influence, for many patients suddenly become affected after discovering the passage of the segments. Berenger-Feraud gives a long list of ailments supposed to result from the presence of tapeworms. Among the nervous manifestations may be mentioned: epilepsy, chorea, giddiness, amaurosis, and hallucinations. On the part of the digestive tract: nausea, colic, constipation alternating with diarrhea. Boulimia, in the popular mind, is one of the chief symptoms; but professional experience shows this to be unfounded. The species found principally in young

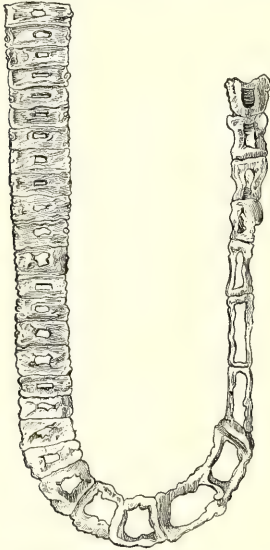
children cause more marked symptoms—convulsions, etc.—on account of the more susceptible age. *Bothriocephalus latus* gives rise, in addition, to a severe form of pernicious anemia—"Bothriocephalus anemia," which arises from intoxication by some poison given off by the worm. Such an anemia is sometimes found when *Tænia saginata* is present, but not with *Tænia solium*. Tapeworms occasionally escape through the bowel and are found in the peritoneal cavity; this occurs *always* through a pre-existing perforation.

The **Nemathelminthes** or round worms have a cylindric body, with the organs contained in a body-cavity. Of the three branches composing them, one is known to be parasitic in man; the other two are uncertain.

Nematoda (*Round Worms*).—The nematodes or round worms proper have long bodies which are not segmented, though sometimes there are external striations. They usually taper off at each end and are provided with a mouth and digestive tract ending in an anus.

The sexes are separate; and the male, as

FIG. 124.—*Tænia fenestrata* (after Léon Colin).



a rule, is smaller. The embryos in most cases are lodged in an intermediate host; in some the definitive host is directly attacked by them.

Ascaris lumbricoides, the common round worm, is a parasite of the small intestine. The male is from 15 to 25 cm. in length, the female from 20 to 40 cm.; the latter is also thicker and three or four times as abundant. The body is yellowish gray or reddish in color, with fine transverse striations; the anterior end is furnished with three papillæ. The posterior extremity of the male is recurved and provided with two spicules; that of the female is plane and without spicules. The eggs are easily recognized (Fig. 125) and very numerous in the feces; they measure from 0.05 to 0.06 mm. in length and have a thick shell enclosed in a brown albuminous capsule. The eggs develop very slowly and may live for five years in a suitable environment.

This species is rarely found single, two to six individuals being usually met with, and from this up to from 300 to 500. It is very often seen with other parasites, especially the other round worms. From 1 to 5 years of

age, the percentage of individuals affected is 10.09 ; from 15 to 20, 27.58 ; and from 45 to 50, 15.12. The round worm is greatly given to wandering and may get into the stomach, nares, glottis, Eustachian tube, pancreatic and biliary ducts. It may perforate the alimentary canal and escape into the urinary organs or through the walls of the body after an abscess has been formed—about the umbilicus in children, the groin in adults. No intermediate host is necessary ; infection occurs through swallowing the eggs in water or food, or through geophagous habits in young children when creeping about. In many cases no symptoms are produced, especially if but few individuals of the worm are present. In young children and nervous individuals it causes considerable disturbance, both reflex and direct—convulsions, vertigo, impaired sight and hearing, colic, vomiting, itching of the nose, etc. In the biliary passages it produces obstruction, then dilatation, with structural changes and jaundice. Sometimes large masses of worms accumulate, giving rise to intestinal obstruction and requiring laparotomy, as in a recent case of Wyeth's (New York). The round worm is cosmopolitan, extremely frequent in some countries (90 per cent. of the Japanese are

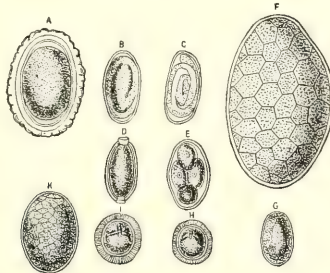


FIG. 125.—Eggs of various worms found in the alimentary canal of man: A, *Ascaris lumbricoides*; B, C, *Oxyurus vermicularis*; D, *Trichocephalus dispar*; E, *Ankylostoma duodenale*; F, *Fasciola hepatica*; G, *Dicrocoelium lanceolatum*; H, *Tænia solium*; I, *Tænia saginata*; J, *Bothriocephalus latus*. $\times 400$.

affected, Bälz), especially in the tropics ; its frequency diminishes as we leave the equator. It is more common in country districts, owing to the use of unfiltered water ; and Blanchard states that in the early part of the century one-half the inhabitants of Paris were infested with the worm from this cause.

Ascaris canis (*Ascaris mystax*) is a common parasite of the small intestine of the cat, dog, and other carnivora. This species is smaller than the preceding, the male being from 40 to 60 mm. in length and the female from 60 to 100 mm. It is easily distinguished by two wing-like folds from 2 to 4 mm. in length, one on each side of the anterior extremity. Eight cases of its occurrence in man are known, but no serious symptoms appear to be produced.

Ascaris maritima has been found as an immature form in a child in Greenland.

Oxyurus vermicularis, the seat- or pin-worm, is a small species, the male being about 4 mm. in length and the female about 10 mm. The posterior end of the male is blunt and curved, that of the female is sharp (Fig. 126). The egg is 0.050 by 0.024 mm., oval and flattened on one side. No intermediate host is necessary ; hence, like *Ascaris lumbricoides*, it is sometimes

endemic in barracks, prisons, and similar communities. The seat-worm is more common in children and in females, and with other parasites is found frequently in immense numbers in the small intestine and occasionally in the



FIG. 126.—*Oxyurus vermicularis*: a, female; b, male (natural size) (Mosler and Peiper).

appendix. After the females have become impregnated, they descend to the large intestine. Individuals often escape from the anus and penetrate to the prepuce and urethra, and to the vulva, vagina, and even into the uterus. This species gives rise to bloody diarrhea and to various nervous symptoms already alluded to in considering other worms. The principal manifestation is an intolerable pruritus coming on after the patient is warm in bed, which is due to the irritation kept up by the sharp tail of the female. This leads to eczema and masturbation in some cases. As reinfection easily

occurs through the fingers, the parasite may persist for many years or for life. The worm is found throughout the world.

Eustrongylus visceralis (*E. gigas*), the giant strongyle, is a very long worm inhabiting the urinary organs of various mammals, especially the dog. The body is reddish, cylindric nearly throughout, the male being from 15 to 35 cm. in length, the female from 25 cm. to 1 meter. The male has a single spicule at the end of a copulatory pouch which is easily recognizable. The kidney is sometimes entirely destroyed by the parasite. Blood-clots passed by the urethra are frequently mistaken for it. It is found in many parts of Europe, North and South America, but is nowhere common. Nine or ten cases of its presence in man are on record.

Strongylus apri (*S. paradoxus*, *S. longæ-vaginata*), a small white worm found in the lungs of the hog; the male is 15 to 17 mm. in length, with two spicules at the posterior end, the female 26 mm. It was found once in the lungs of a child, and once in the alvine discharges of an adult.

Strongylus subtilis is a very slender worm recently discovered by Loos in Egyptian natives. The male is about 4 mm. long, the female 7 mm. Its habitat is the upper part of the small intestine, where the females are much more abundant; the mouth is unarmed. No pathologic effects are attributed to it.

Ankylostoma duodenale (*Uncinaria duodenalis*, *Dochmius duodenalis*), the cause of ankylostomiasis, "miners' anemia," "tunnel disease," or Egyptian chlorosis, is a very small round worm, the male

from 6 to 11 mm. in length, the female from 15 to 18 mm. (Fig. 127). The color varies from white to red, according to the amount of blood in the body. The head is provided with six teeth and a sucking apparatus. This species inhabits the small intestine and is usually found within two meters of the pylorus, occasionally two or three meters lower down, seldom in the stomach. The head and often part of the body are firmly buried in the mucous membrane, and



FIG. 127.—*Ankylostoma duodenale* (natural size) (after Schultheiss): a, b, c, females; d, e, f, males.

sometimes cannot be dislodged even at a necropsy. Sandwith, of Cairo, who has had unusual opportunities for observing ankylostoma, found 863 individuals to be the maximum in 400 cases.¹ They are, however, often

¹ *London Lancet*, p. 1362, June 2, 1894.

found in much larger numbers—into the thousands. Grassi calculates that for every 150 or 180 eggs in a cubic centigram of feces, 1000 worms are present. The proportion of males to females is about 1 to 3. The worm is supposed to live several years. Infection occurs from earth containing the embryos being carried to the mouth, either on the hands or with the food. Drinking-water seems to be a less important source of danger.

This species, though small, is one of the most formidable parasites infesting man. It is widely distributed in Italy (in 20 per cent. of the necropsies in Milan), Switzerland, Germany, Austro-Hungary, Egypt, Abyssinia, India (75.5 per cent. of 1249 natives, Dobson), Japan, Borneo (100 per cent.), Java; also in Brazil, Guiana, the Southern United States, and Porto Rico. If few worms are present, the pathologic effects are not marked; if many hundreds are present, a grave anemia with the characteristic signs appears.

In discussing this anemia, Rogers¹ shows that it is characterized by: 1. A much greater reduction of hemoglobin than of the number of red corpuscles, and consequently a very low hemoglobin value. 2. The white cells also are reduced in number, but relatively to the red cells they are increased. 3. The specific gravity is greatly reduced after allowing for the amount of reduction of the hemoglobin. In 12 cases the per cent. of hemoglobin averaged 15.16. The red cells were 2,145,000 per cubic mm., the hemoglobin value of each red corpuscle being only 0.31 as against 0.65 for healthy natives or even those suffering from malarial anemia; so these two anemias can be differentiated. The ratio of white cells to red cells was as 1 to 524, and the specific gravity was 1034.

The local changes are thickening of the mucous membrane, with mal-assimilation and chronic starvation. Pure blood is not seen in the stools, and bloody mucus only occasionally, the blood being so mixed with the bowel contents that it is seldom distinguishable.

Trichocephalus dispar (*T. trichiurus*, *T. hominis*), the whip-worm, has a body composed of two unequal parts; the anterior three-fifths is no thicker than a thread and contains only the esophagus; the posterior two-fifths is



FIG. 128.—*Trichocephalus dispar*: a, female; b, male (natural size) (Heller).

much thicker. In the male it is wound up into a spiral, in the female it is slightly curved; the total length of the former is from 35 to 45 mm., of the latter from 35 to 50 (Fig. 128). The usual habitat is the cecum, also the appendix and the first part of the colon. While generally free in the bowel, the anterior end often transfixes the mucous membrane like a pin. From 6 to 20 individuals is the rule, sometimes 150; rarely more are found. Both sexes are affected, and all ages except very young children. No intermediate host is required, and Grassi infested himself by swallowing the eggs; after a month's time he discovered eggs in his stools. The whip-worm is

¹ *Jour. of Pathol. and Bacteriol.*, v., p. 399, 1898.

cosmopolitan in distribution and extraordinarily frequent in hot climates (90 per cent. of the inhabitants of Cachar, India, are affected—Powell). As a rule, no pathologic effects seem to be caused by this species, although occasionally it excites the usual reflex nervous symptoms. Rokitsansky believed it to be the cause of enteric fever.

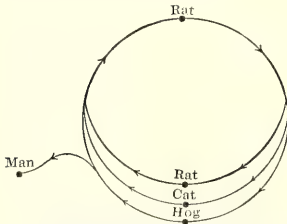


FIG. 129.—Life cycle and intermediate hosts of *Trichina spiralis* (after Bollinger).

Immediately after infection, the males are less numerous and soon die, leaving females alone present. In three or four hours after eating raw or insufficiently cooked pork, the young worms are found in the stomach; they pass hence to the small intestine, arriving at sexual maturity in three or four days (Fig. 129). Many of the embryos escape with the feces; the others ultimately rest either in a muscle-fiber or between the fibers. The capsule



FIG. 130.—*Trichina spiralis* encysted in muscle. Teased fresh specimen.

containing the muscle-trichina is about 0.40 mm. in length, usually oval, sometimes round, parallel with the long axis of the fibers (Fig. 130), and at first clear, but eventually calcified. Only one worm is found in a capsule, as a rule, though as many as seven have been met with; one gram of muscle has been estimated to contain from 12,000 to 15,000 embryos. The cysts may live for many years without becoming calcified—in man 12 years, in the pig 11, 20, and 24 years; they survive exposure to extreme heat and cold ($+80^{\circ}$ and -25° C.). Two views are held as to the origin of the cyst: one that it is formed by the

sarcolemma, the other that its presence causes proliferation of the connective tissue. The old view that the embryos bore their way through the intestinal wall has been disproved by Askanazy and Cerfontaine, who found that the female itself penetrates the wall and the embryos are born directly into the lymph-current.

When the embryos are first freed they give rise within a day to intense gastro-intestinal irritation with vomiting and diarrhea, the attack bearing some resemblance to enteric fever. On their migration they cause myositis with severe muscular pains and high fever. At first there is edema of the face, especially of the eyelids; later on of the trunk and limbs, not involving the genital organs. The attack is at its height in two to four weeks after infection, and either death or subsidence occurs. The muscles of the upper

half of the body are more frequently the location of the cysts—the diaphragm (especially its pillars), the intercostal and lumbar muscles, the tongue and eye; the heart seems to escape. In the muscles they are found mostly at the tendinous ends, and are less numerous in the limbs as the periphery is approached. Besides muscles, lymph-glands are also involved. As the hosts of the trichina—the rat and hog—have a world-wide distribution, it also has a wide range, but great local differences exist. Thus it is not frequent in England, France, or Italy. It is common in Holland, in Germany (of 4,421,208 hogs examined in Prussia in 1885, 2387 had trichiniasis), and in the United States (estimated at 2 to 3 per cent. of hogs). The German custom of preparing dishes from partly cooked pork has been responsible for many so-called “epidemics.” Two of the most destructive occurred in Saxony. In 1865, in the village of Hedersleben, with a population of 2000, 337 persons were attacked, with 101 deaths. In 1884, in the villages about Emersleben, with a population of 1600, the flesh from one hog gave rise to 256 known cases, with 52 deaths.

An important diagnostic point in trichiniasis is the discovery by Brown¹ of a marked increase of eosinophilic cells in the blood, which can be made use of at once. Osler shows that sporadic cases are much commoner than hitherto supposed, and that the eosinophilia is an important point in diagnosing obscure cases.

Filetia medinensis (*Dracunculus medinensis*), the guinea-worm, the cause of dracontiasis, has been known since the days of Moses, for it is evidently the “fiery serpents” mentioned in the Bible. The male has only lately been discovered and is much smaller than the female, which is from 60 or 80 cm. to 1 meter in length. The body of the latter is yellowish white in color, very extensile, and consists mostly of the uterus, which is closely packed with small embryonic worms. The connective tissue in any part of the body is the habitat of this species, and while as many as thirty have been seen in the body at one time, a single worm is the rule. In 98 or 99 per cent. of the cases the worm appears in the lower limbs. (In a patient with seven worms, three were in left leg, two in left foot, one in right leg, and one in right forearm. In another with thirteen, four were in left foot, two in right foot, two in left leg, one in right leg, one in right thigh, and three in right forearm—Lorimer.) It may appear anywhere—orbit, mouth, ears, eyelids, etc., but these locations are very rare. The female, when mature, wanders through the tissues until the skin is reached; a small vesicle forms over the head, which ruptures in a few days, revealing the worm at the bottom. The embryos are discharged through this for a week or two, by which time the uterus is empty and the parent quits the host or can be extracted. Clumsy attempts at extraction—rolling up the worm on a stick, etc.—frequently pull it in two, with disastrous results; for the embryos, escaping into the tissues, cause abscess-formation, sloughing, and the limb very often requires amputation. Fedschenko has proved that the embryo penetrates the familiar fresh-water crustacean Cyclops and becomes metamorphosed in a month. Hence drinking-water is probably the means of infection. In man the worm requires a year or eighteen months to attain maturity. The guinea-worm is widely distributed in the tropical regions of Asia and Africa, also in Brazil.

Filetia Sanguinis Hominis.—Under this name, Lewis, of Calcutta, in 1872 described a parasite of human blood which was first noticed in 1863

¹ *Jour. Exper. Med.*, iii., p. 315, 1898.

by Demarquay. We owe to Manson's researches the discovery that there are five or six different species included under this designation. Some of these are found in the blood at night, others in the day, and still others all the time. The periodicity in the nocturnal forms is constant; it continues night after night with unvarying regularity for years. Its object, according to Manson, is to adapt the habits of the parasite to those of its intermediate host, the mosquito. The same observer discovered that the embryos which leave the cutaneous circulation in the day are found partly in the larger arteries, but the vast majority in the pulmonary blood-vessels.

Filaria Sanguinis Hominis Nocturna.—The embryo is about 0.3 mm. in length, transparent, with a pointed tail, and enveloped in a sheath which is longer than the animal and projects beyond it at one or both ends (Fig. 132). This species is found in both tropical and temperate climates, in the latter in new arrivals from warm countries. It is especially frequent in some districts—Bahia (10 per cent. of population), Cochin-India (30 per cent.), Samoa and Fiji (50 per cent.—Thorpe). In the United States it is found in Virginia, South Carolina, and Alabama. The filariæ appear in the cutaneous circulation about five or six o'clock in the evening, and increase up to midnight; after that they gradually decrease until by eight or nine o'clock in the morning they have nearly all disappeared, to come forth in the evening again. If the sleeping and waking hours be reversed, the filarial periodicity is also reversed. As many as 300 parasites have been found in a single drop of blood; they are also found in the urine and tears.

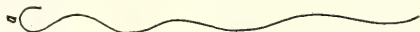


FIG. 131.—*Filaria sanguinis hominis*, adult female (natural size) (after Cobbold).¹

The female mosquito acts as the intermediate host. The parasites in the cutaneous circulation are sucked up and enter the body of the mosquito, where they are metamorphosed. In about a week's time they escape into the water, on the death of the mosquito after laying its eggs. Gaining access to the human stomach in the drinking-water, they bore through the tissues and become sexually mature in the lymph-vessels, whence the embryos are carried into the blood through the thoracic duct.

Filaria Bancrofti is the parent form of *F. nocturna*, and inhabits the lymph-vessels. The male is transparent and about 70 mm. in length; the female is brownish, very thin, and measures 90 mm. (Fig. 131). Embryo filariæ (*F. nocturna*), so far as known, cause no pathologic effects, but *F. Bancrofti* produces marked changes by blocking the lymphatics. If the occlusion is only partial, a lymph-varix is the result, evidenced by lymph-scrotum, varicose lymphatic glands, chyluria, chylous ascites, or chylous accumulation in the tunica vaginalis. When the obstruction is complete, the lymph-trunks may burst with ensuing lymphorrhagia, or the lymph accumulates in the tissues, which are first edematous, then firmer, and elephantiasis Arabum develops.¹

Filaria sanguinis hominis diurna is a worm known only in the embryonic state, in which it is very similar to *F. nocturna*, and is found in negroes on the west coast of Africa. Unlike the latter, it is only present in the blood in daytime, commencing to appear at eight or nine o'clock in

¹ For illustrative case, see Report of Two Cases of Filariasis, by Lothrop and Pratt, *Am. Jour. Med. Sc.*, cxx., p. 525, 1900.

the morning, increasing until noon, and disappearing about eight or nine o'clock in the evening. It is said *Filaria loa* is the parent form of this variety. The intermediate host must evidently be some diurnal species, but the exact one is unknown as yet.

Filaria loa is about 25 mm. in length in the male, and 30 to 40 mm. in the female. It occurs in the subcutaneous connective tissue and is often found about the bridge of the nose, also under the conjunctiva. It is a native of the west coast of Africa, occurring over the same area as its supposed embryo, *Filaria diurna*. It has been noticed in persons absent from that country for over ten years. When located in the eye, it causes great pain.

Filaria sanguinis hominis perstans is much smaller than the other filariæ, both in length and thickness. It is about 0.25 mm. in length, has no sheath, but is provided with a retractile proboscis and is not periodic. It is not very numerous, and three or four individuals to the slide is the average. It may be found with either *F. nocturna*, *F. diurna*, or both; its habitat is the west coast of Africa. Recent investigations render it probable that a blunt-

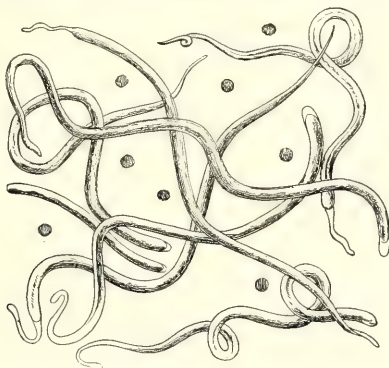


FIG. 132.—Embryos of filaria circulating in human blood. $\times 500$ (after Lewis).

tailed species from British Guiana is the parent form of this variety. If this be confirmed, *F. perstans* is endemic to both tropical America and Africa. Manson believes this worm is the cause of the "sleeping-sickness" or "negro lethargy." He thinks this is rendered probable by the fact that the organism has often been found in the blood in this disease.

Filaria Demarquaii has been found in the blood of negroes in the West Indies. The embryonal form, which alone is known, is smaller than *Filaria nocturna*.

Filaria volvulus inhabits the lymphatics of the subcutaneous tissue. The male is 30 to 35 mm. in length, the female 60 to 70 mm. The nodular swollen lymphatics form masses under the skin as large as a pigeon's egg, which increase in size with the growth of the parasite.

Filaria Magalhæsi was found in the heart's blood of a child in Brazil. It is thought possibly this may be the parent form of *Filaria Demarquaii*.

Filaria Ozzardi is found in British Guiana. *Filaria lentis* has been found several times in the crystalline lens. Several other species of *Filaria*

have been described—*F. conjunctivæ*, *F. restiformis*, *F. labialis*, *F. hominis oris*, etc.—but the limits of space forbid any detailed allusion.

Strongyloides Intestinalis (*Anguillula Stercoralis*, *Rhabdonema Intestinale*).—This parasite was discovered by Normand in the subjects of Cochin-China diarrhea. It occurs under two forms: the smaller, the one formerly called *Anguillula stercoralis*, is about 1 mm. in length, the anterior extremity being truncated, the posterior sharp; the larger (*R. intestinale*), of which the female alone is known, is 2.2 by 0.034 mm., similar in shape to the smaller form. The large form is always found in the intestine and gives origin to large parthenogenetic ova, which develop into male and female in water (alternate generation), and man becomes infested through drinking water containing the ova. When these are swallowed, the intestinal form (*Rhabdonema intestinale*) develops, and so on. The intestinal form lives in the mucus of the upper part of the small bowel, and is not now considered of any pathologic importance; its occurrence in severe tropical diarrhea is a coincidence.

ARTHROPODA (Insects, etc.).

This enormous group comprises the insects and other forms with jointed legs. Of the multitude of species composing it, but few are parasitic on man.

Linguatulida.—These are parasitic arthropods with a long round or flattened body composed of rings. The sexes are distinct and the head is furnished with hooks.

Linguatula Caprina (*Pentastoma Tænioides*, *P. Denticulatum*).—The larval form, *P. denticulatum*, is from 4 to 5 mm. in length by 1.5 mm. in

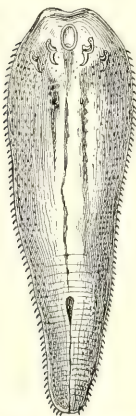


FIG. 133.—*Linguatula caprina*
(larval form).

width; the body is made up of 9 or 10 segments, the outer surface being covered with small spines; the mouth has four hooklets. It infests the herbivora; in man it has been found enclosed in a capsule in the spleen, liver, kidney, lung, and intestine. It is frequent in some countries, *e. g.*, Germany (30 times in 200 necropsies—Zenker; 5 in 47—Frerichs), but appears to have no pathologic importance. The adult form, *Pentastoma tænioides*, has a whitish lancet-shaped body, the male being from 15 to 17 mm. long, the female from 60 to 80 mm. The body is made up of 80 or 90 segments, covered with fine spines directed backward. It infests the nasal fossæ, frontal and maxillary sinuses of the dog and other carnivora. When the larval form in the rabbit or hare is eaten by a carnivorous animal, the larvæ make their way to the nose, become sexually mature, and cause epistaxis and sneezing, which scatters the eggs abroad; these fall in the herbage, are eaten by the rabbit, become encysted in the flesh, ready to undergo the same changes. Only one or two doubtful cases are on record of its occurrence in man.

Porocephalus constrictus (*Pentastoma constrictum*) is only known in the larval state. It is much larger than the larval form of the preceding, being

from 10 to 13.5 mm. in length, with a white cylindric body, which has from 20 to 23 segments and two pairs of hooks; the surface is smooth. It is found coiled up in cavities in the liver and lungs, and is found free in the peritoneal cavity and in the intestinal canal. It has been seen several times in negroes, in Africa and elsewhere. The source of infection is unknown. It produces great irritation and apparently sometimes causes peritonitis.

Acarina (including *Mites and Ticks*).—*Demodex folliculorum* is found in the sebaceous glands, especially those of the face, also in the ceruminous and Meibomian glands. The male is 0.30 mm. in length, the female 0.36 to 0.40 mm.; the body is smooth, segmented, with four pairs of limbs and a proboscis. If numerous, it causes comedones and acne. The number in a normal gland is 1 or 2, in the comedones up to 15 or 20. These mites are found at all ages except in very young children.

Sarcoptes scabiei, a small parasite, the male 0.20 to 0.25 mm. in length, about one-third as large as the female, reddish gray in color. The itch-parasite lives in burrows in the skin, 0.5 to 3 mm. in length usually, sometimes much longer (Fig. 134); each burrow contains one female, which lives two or three months and lays one or two eggs each day. These are partly segmented when laid, and the young are hatched in less than a week. The burrowing of the female causes intense itching, and excoriations and eczematous eruptions are produced by scratching. Almost any part of the body may be attacked by the parasite, which is found throughout the globe.

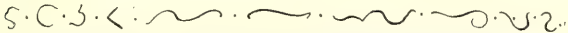


FIG. 134.—Various aspects of the track of *Sarcoptes scabiei* (after Hardy).

Scabies is easily communicated, both by personal contact and by clothing. The itch-mites from other animals may infest man, usually only for a short period—from the cat, hog, horse, goat, and camel.

Among other mites are *Tyroglyphus siro*, the cheese-mite, occasionally found in the stools; *Glyciphagus domesticus*, the sugar-mite, causing "grocer's itch"; *Aethrobium farinae*, the flour-mite, etc.

A great number of ticks attack man and animals; they suck the blood and cause intense itching, with skin-eruptions, sometimes suppuration and lymphangitis. Various species of *Ixodes*, *Trombidium*, and other genera occur as parasites.

Hemiptera.—In this group are several species which have become much degraded as a result of their long parasitic life. The lice are wingless bugs.

Pediculus Capitis.—The head-louse is exceedingly prolific; Leeuwenhoek calculated that an adult female will produce about 5000 eggs in two months. The nits hatch about the sixth or seventh day, and in three weeks' time the young are capable of reproduction. The color varies with the race of man; in the dark races they are always much darker than in the Caucasian. When transported from one race to another, they die in a short time. Head-lice are a frequent cause of enlarged cervical glands in children, which sometimes suppurate. *P. vestimenti* is probably the same species as the preceding. *P. pubis* is found principally in the white race. According to Moursou, the "tâches bleuâtres" are due to the bites of this species.

The discoloration appears about the punctures, stays a few days, and then disappears.

Diptera.—Before proceeding to the flies proper, the degenerated forms, the fleas, require a short notice.

Pulex irritans, the common flea, is found on man alone, but occasionally quits him for a short stay on the domestic animals. This species is found over the whole world.

Sarcopsylla penetrans is the sand-flea or "chigger." The males and non-pregnant females are 1 mm. in length, and are only occasionally parasites seeking man to suck his blood. The impregnated female buries herself, head first, in the skin of man and animals. By the growth of the eggs the abdomen increases to an enormous size, and the skin over the animal becomes red, inflamed, and finally ulcerates. This species is common in tropical America, whence it has extended to West Africa and recently to South and East Africa. Sometimes 50 to 60 individuals are found in the body at once. It attacks the lower extremities by preference, and causes onychia, ulcers, and phlegmonous inflammations. The ulcers and cavities often lead to inoculation with tetanus.

Various species of *bot-flies* (*Oestrus*) are found under the skin, producing a swelling which becomes inflamed and from which the larva ultimately escapes or is extracted. In the Southern States and in South America, the screw-worm (*Lucilia macellaria*) commits great ravages. The eggs are laid in the nasal fossæ, maxillary and frontal sinuses, or the ears, especially of persons with ozena or otitis. The larva is provided with hooks at the anterior end, and the body has circles of spines, giving it the appearance of the thread on a screw (Fig. 135). This form destroys the mucous membrane, periosteum, and other soft parts, and even the bones. In 44 cases there were 30 deaths.



FIG. 135.—Larva of *Lucilia macellaria* (after Conel).
× 4.

Before leaving the subject, attention must be directed to the propagation of disease by insects, as maintained by Nuttall and others. As a result of experiments by various investigators, it is definitely proved in some cases, and rendered extremely probable in others, that various infectious diseases may be carried by insects, *e. g.*, Texas fever in cattle, anthrax, cholera, enteric fever, plague, tuberculosis, etc. In addition, the mosquito has been shown by a host of observers to be the chief agent in the propagation of malaria. The literature of the past few years contains numerous references to this subject. Animal as well as vegetable parasites are transported by insects.

PSEUDOPARASITISM.

A good example of this is furnished by Scheiber's case. A woman in Hungary, with nephritis, passed urine containing albumin, a little blood, and numerous minute worms. These were present by thousands daily, and proved to be *Rhabditis pellio*, a species inhabiting damp earth and putrefying organic substances. On investigation it was found that the Hungarian peasants make use of earth poultices to relieve pain. The patient had applied earth to the thigh, whence the worms had entered the vagina and

multiplied. Hysteric individuals frequently pretend to pass earthworms and similar objects. Among other pseudoparasites are substances found in the urine or feces, which were in the vessel originally and did not come from the body at all. Blood-clots or strings of mucus evacuated with the urine are frequently mistaken for worms, as are shreds of membranes, vegetable tissues, or partly digested flesh in the stools.

The condition known as myiasis is due to swallowing the eggs of flies, in food or otherwise. The larvæ develop in the intestine and are discharged from the bowels. The flower-fly (*Anthomyia canicularis*) is one of the most common species, sometimes two or more liters of the larvæ being passed by a single patient. More than fifteen species are known to infest man. They give rise in some cases to colicky pains and diarrhea; in others no inconvenience is experienced. Blanchard¹ has collected 35 cases of pseudo-parasitism of some 10 different species of the common "thousand-legs"; 27 cases were in the nasal fossæ and neighboring cavities and 8 in the alimentary canal.

¹ *Arch. de Parasit.*, i., 452, 1898.

INTOXICATIONS.

INTRODUCTION.

Definition.—A poison is a substance of definite chemical composition, which by virtue of its constitution is capable, when brought in contact with the tissues of the body, of modifying the cellular activity of one or more organs to such an extent as to impair health or destroy life. This definition excludes all substances which cause injurious effects on account of their physical properties. Powdered glass taken into the stomach might cause death, and yet it would not properly be called a poison, since the resulting injury is due to the physical properties and not to the chemical constitution of the glass. Life may be destroyed by burns from hot air, water, or metal; and yet in such a case the air, water, or metal could not be considered a poison, because the ill effects are due to the temperature of these substances. This definition excludes bacteria and animal parasites. These may elaborate bodies that are harmful by virtue of their chemical composition, and they may contain such substances within themselves, but the bacterial cell cannot be regarded as a chemical compound.

Sources of Poisons.—Poisons may be grouped according to the sources from which they come, as follows:

Mineral: as arsenic, lead, phosphorus, etc. Many substances derived from the mineral world owe their poisonous properties to certain artificial changes to which they have been subjected. Silver, as it is found in nature, is inert; but in the form of the nitrate it becomes quite active. While some of the phosphates and phosphites are injurious to the body when employed in large doses, their action is hardly comparable with that of the isolated phosphorus, in which form this element does not occur in nature.

Synthetic: as anilin, nitroglycerin, antifebrin, etc. The discoveries of the synthetic chemist have demonstrated the fact, long denied, that the toxicologic action of a substance is determined by its chemical composition. Indeed, we are now able to predict within certain limits the physiologic action of a compound from a knowledge of its chemical structure, and this action can be modified by the substitution of one group of atoms for another. The possibility of thus building up new substances capable of inducing modified or even radically different effects seems to be unlimited, and this branch of chemistry is still quite new. Additional discoveries along this line will probably greatly advance our knowledge of the science of toxicology.

Vegetable: as morphin, strychnin, abrin, ricin, etc. These are chemical compounds that result from the activity of plant-cells. Poisons originating in this way are capable of many subdivisions on the basis of their chemical composition. We have the vegetable alkaloids, the poisonous acids of vegetable origin, as oxalic acid, and the poisonous glucosids and vegetable albumins.

Bacterial : as tetanin, the diphtheria toxin, and other bacterial toxins. These again are capable of subdivision, as the basic poisonous bacterial products, or the ptomaines, and the so-called toxalbumins. In reality the bacterial poisons belong to the foregoing group, inasmuch as bacteria are vegetable organisms.

Animal : as the venom of serpents, the poisonous secretions of certain fishes, the poisonous leukomains, etc. These also may be subdivided. Some of them are not poisonous to the animal in the body of which they are generated, but act as poisons upon the tissues of other animals ; while others act injuriously when allowed to accumulate unduly in the organism in which they originate.¹

MINERAL POISONS.

Arsenic.—To the cells of the higher animals, arsenic is a universal poison. So far as we know, there is no vertebrate immune to its action, although susceptibility varies within wide limits. Not only are all of the higher animals susceptible to arsenic, but it is poisonous to all kinds of tissues. It produces deleterious effects when applied to the unbroken skin, when it comes in contact with mucous surfaces, when administered subcutaneously or by mouth, and when inhaled in the gaseous form. When applied locally in sufficient quantity, it causes necrosis of tissue. It may alter the composition of the blood, cause atrophy of the muscles, modify the growth of bone, and induce pathologic changes in the nerves. Loew found that algæ and certain infusoria grow in neutral solutions containing 1 part of arsenic to 1000 of water. He concludes from his experiments that, to the lowest forms of animal life and to many of the lower plants, arsenic is not a poison. Arsenous acid may kill the lower forms of life ; but it does so by virtue of its acid reaction, and not on account of its arsenic content.

Authorities are not altogether in harmony concerning the *modus operandi* of this poison. It is generally believed that it induces cellular death by its direct local effect as an irritant. Its corrosive action has been attributed to the supposed avidity with which it is said to combine with albumin ; but Binz and Schulz claim that there is no albuminate of arsenic, and that it has, properly speaking, no corrosive action. These authorities teach that the poisonous action of arsenic is due to the readiness with which it gives off and takes up oxygen. Arsenous acid is a reducing agent, while the *arsenic* compound is equally effective in causing oxidation. They show that various animal and vegetable substances, at body-temperature, reduce arsenic acid to arsenous acid and oxidize the latter to the former. Both of these processes are quickly wrought, both within and without the body. The sudden and continued withdrawal of oxygen from one molecule and its transference to another are believed by Binz to be the true explanation of both the therapeutic and toxic action of arsenic. Binz states that the most important lesions induced by arsenic are found in those tissues which are specially endowed with the function of receiving and utilizing the oxygen of the blood, such as the glandular

¹ It is impossible, in a work on general pathology, to discuss all poisons. The writer has therefore selected a few of the most important. Moreover, he has confined himself to a description of the pathologic changes induced in the body by these substances. He has not lost sight of the fact that this is a chapter in a work on pathology. The chemistry of poisons and the symptoms induced by them have been omitted, so far as possible, as not being in place in a work of this kind.

protoplasm. A parallel to this is believed to exist in the action of certain oxids of nitrogen. NO is said to be poisonous because it takes up oxygen, and NO₂ is poisonous because it gives off oxygen. A more interesting example of this kind of action is shown in the preparation of anilin black. Anilin chlorid and potassium chlorate are mixed; but no change takes place until a small bit of ammonium vanadate is dropped into the mixture, when all of the anilin is changed into anilin black. The vanadium compound takes oxygen from the chlorate and transfers it to the anilin. One part of the vanadate may in this way produce 20,000 parts of anilin black. This interesting theory of the action of arsenic may be designated as the theory of "the oscillatory molecule of oxygen."

It has been held, especially by certain French writers, that arsenic owes much of its poisonous action, if not all, to its effect upon nervous tissue, in which it has been believed to replace phosphorus. This theory is founded upon the belief that arsenic is deposited in large amount in the brain, which is certainly erroneous. Many investigators have shown that the amount of arsenic in the brain, after poisoning with this substance, is much smaller than that found in the liver and kidneys. In 1884 the writer found this to be true, both in acute and chronic poisoning with white arsenic, and in acute poisoning with the more soluble preparations.

Chronic arsenic poisoning is frequently accompanied by the development of some lesion of the skin. Arsenic rashes, generally accompanied by itching, are for the most part of the erythematous type; but papules, vesicles, pustules, ulcers, and gangrene have been reported. The long-continued therapeutic administration of arsenic is sometimes followed by a pigmentation of the skin, which is generally most marked over the upper covered portions of the body, but may extend to the hands and face. The effects of arsenic on the skin have led to the supposition that this poison is eliminated through the skin; and Brouardel and Pouchet have detected arsenic in the skin, nails, and hair of persons poisoned with it. Rarely there is observed a form of cutaneous pigmentation known as arsenic melanosis. This is due to the deposition of a nonarsenic decomposition-product of hemoglobin in the skin. The skin becomes dark brown; and this special coloration is most marked, as a rule, over the neck and extremities, although it has been observed in the axillæ and popliteal spaces. Microscopic examination shows reddish, brownish, or black granules about the lymph-vessels of the papillæ. In very rare instances this pigment is deposited so abundantly that it forms small tumors. Chemically this coloring matter is identical with the bilirubin of the bile and with the hematoidin crystals found in various parts of the body where there have been extravasations of blood.

While poisonous doses of every form of arsenic have more or less destructive action on the coloring matter of the blood, this effect is most marked when the poison is inhaled in the form of the arsenid of hydrogen. The urine becomes dark red and even black, from the rapid disintegration of the red corpuscles. Formed elements in the urine, such as epithelial cells and spermatozoa, may be stained brownish red or yellow. The broken-down hemoglobin is converted into bile-pigment so rapidly that icterus is soon observable, and after twenty-four hours the skin may be quite thoroughly bronzed. Stadelmann studied the action of this poison on dogs with biliary fistulæ, and found that the amount of bilirubin was increased twenty times.

The nervous system is markedly susceptible to the action of arsenic. Arsenic paralysis may result from either acute or chronic poisoning, and from internal administration or external application. There may be no evidence of it after large doses, and it may result from relatively small quantities. Why it appears in some cases of arsenic poisoning and not in others has never been satisfactorily explained. Jaccoud thought it most common in alcoholics, but this has been denied by others. The paralytic affections vary in intensity from slight weakness to complete loss of motion. They may be transitory or permanent. They set in with the first symptoms of gastric irritation or may be tardy, first appearing weeks after other symptoms have manifested themselves. Disturbances of motion are generally confined to the extremities, but there are some cases reported in which the muscles of the trunk have been involved. The four extremities are affected in most instances, but the legs are more frequently involved than the arms. Sometimes there is hemiplegia, but more often the paralysis is symmetric. The paralysis is most marked in the distal parts, the fingers and toes, growing less evident nearer the trunk. Paralysis is always associated with muscular atrophy, which is characterized by its early appearance and rapid development. The atrophy may be degenerative or simple. Diminished response to both faradic and galvanic stimulation is observed.

The marked atrophy of the muscles of the extremities gives to the patient a peculiar appearance. Especially in cases following acute arsenic poisoning, it happens that the face and trunk appear perfectly healthy, while the limbs are shrunk, the subcutaneous fat on them has disappeared, and the nails are diseased or have fallen out. The skin of the extremities is withered and dry, except over the hands and feet, which are often bathed with cold perspiration. Sometimes there are ulcers. Edema is rarely observed. The tendon reflex is absent in all cases; the skin reflex has not been well studied. In some cases there are contractures, especially of the knee-joint. These are due to unequal involvement of individual groups of muscles. Disturbances of sensation accompany those of motion, and sometimes the former predominate. Pain is rarely absent; in many cases it becomes the most distressing symptom.

The histologic changes which accompany these abnormalities of motion and sensation have not been closely studied. It was formerly believed that arsenic induces a myelitis. The theory that arsenic replaces the phosphorus in nervous tissue has already been referred to, and has been found to rest upon insufficient evidence. Popoff concluded from his experiments upon animals that arsenic induces a central myelitis and that the peripheral nerves remain unaffected; but more recent studies show that the changes occur in the nerves and that arsenic polyneuritis does not differ from that induced by other toxic agents. There are proliferative changes in the neurilemma-cells, and the inflammation may be exudative. Regeneration may occur, as it does after experimental division of nerves.

Cases of paralysis of nerves not usually involved are known. Such are the instances of *anaphrodisia arsenicalis* reported by Bielt and later by Charcot, also of paralysis of the vocal cords observed by Mackenzie.

The brain and cord do not always escape the direct action of arsenic. This is shown both by the symptoms and postmortem findings. In rare instances cerebral hemorrhage has been observed; but usually in the most acute cases hyperemia of the meninges and effusion into the ventricles are the only pathologic changes found in the brain, and these are not constant.

Mummification of the body after death from arsenic poisoning has been frequently observed, and has been regarded by some as valuable evidence concerning the cause of death in cases which have been investigated legally. At least one instance of this kind attracted much attention some years ago, largely because Robert Koch figured as an expert in it. The body was exhumed after the coffin had lain partly in water for eleven months. Traces of arsenic were found in the body, which was markedly mummified. Koch considered the mummification strong evidence in favor of death from arsenic. It was shown that tartrate of antimony containing traces of arsenic had been administered medicinally, and this was supposed to account for the small quantities of arsenic found in the body. Although the accused was found guilty, toxicologists have not agreed concerning the evidence. Arsenic is

generally regarded as a powerful antiseptic, and unfortunately it is a common ingredient of embalming fluids.¹ However, its antiseptic properties have been greatly overestimated, and many bacteria grow abundantly in media which contain much more arsenic than that found in persons poisoned with it. Indeed, in some instances of known arsenic poisoning, the liver and spleen have been found to be unusually soft and yet rich in arsenic. The writer ascertained, in carrying on some toxicologic investigations a few years ago, not only that some germs grow abundantly in the presence of large quantities of arsenic, but that all of the arsenic may be converted into gaseous compounds and given off, leaving the mass of tissue wholly free from arsenic. Too much importance must not be given to mummification as an evidence of arsenic poisoning. Mummification is by no means always due to arsenic, nor are arsenic bodies always well preserved. The vomiting and diarrhea, which are persistent and profuse in most cases of arsenic poisoning, not only empty the alimentary canal, but also materially reduce the water in the body; and to these effects, rather than to the arsenic, is to be attributed the delay in putrefactive changes frequently observed after death from arsenic.

At the autopsy held soon after death from arsenic, the skin is generally cyanotic; and the body may be much reduced in flesh, even in cases of acute poisoning. The mucous membrane of the mouth, pharynx, and esophagus shows no abnormality. In a large percentage of the cases, gastritis is more or less marked. Although the greater part or even the whole of the mucous membrane may be reddened, almost invariably there are areas in which the involvement is deeper than elsewhere. The erosion varies greatly in intensity. It may be confined to the mucous membrane, or it may penetrate all the coats of the stomach and cause perforation. As long ago as 1753, Sproegel showed that these gastric lesions result not only when arsenic is taken by the mouth, but also when it is absorbed from wounds; and since that time they have been frequently induced experimentally in the lower animals by the hypodermic administration of neutral solutions of arsenic. The pathogenesis of the gastric lesions has been a matter of some dispute among toxicologists. It has been generally assumed that the erosions are due to the local action of the poison; but in view of the fact that they are produced by the absorption of arsenic when applied to raw surfaces and follow hypodermic administration, Taylor and others have claimed that arsenic gastritis (and enteritis as well) is a specific effect of arsenic poisoning and is not due to local action. Virchow very properly states that the gastritis of arsenic poisoning cannot be considered specific, for the same condition with cloudy swelling and a tendency to fatty degeneration in the glandular cells of the stomach is observed not only after poisoning with arsenic, antimony, or phosphorus, but also as a result of certain infectious diseases, such as variola. However, this does not explain anything. It only gives a wider interest to the study of the pathogenesis of toxic gastritis. To say that the poison of variola induces in the stomach lesions similar to or identical with those induced by arsenic cannot be accepted as a satisfactory explanation of how the poison in either case causes these pathologic changes. Moreover, it is altogether possible that the mode of action of the two poisons may be unlike, notwithstanding the fact that identical results are reached.

Binz and Schulz have endeavored to explain the gastric lesions in accord

¹ Recently formaldehyd has been substituted for arsenic by many embalmers.

with their theory of the action of arsenic, which has been referred to above. They hold that in the alimentary canal there are certain "predilection" places in which the poisonous action of arsenic is most marked, and that the peptic glands constitute one of these places.

Böhm has suggested that the arsenic lesions of the stomach may be due to partial paralysis of the blood-vessels of this organ. Hermann thinks it possible that arsenic may affect the peripheral nerves of the stomach, and thus indirectly so influence the local blood-supply as to lead to inflammatory changes and even to hemorrhagic erosions.

Filehne found in some experiments upon rabbits that the gastric erosions do occur when the contents of the stomach are kept neutral or alkaline, and he concludes from this that the lesions are due to self-digestion of the walls of the stomach; but he fails to explain how the arsenic makes self-digestion possible.

Of course, when applied in mass to the mucous membrane, arsenic has a locally destructive action. Hoffmann's case illustrates this nicely. He found a putty-like mass of arsenic in the stomach, and, directly under it and of the same size and shape, an erosion. It is also true that arsenic administered hypodermically is eliminated by the mucous membrane; but it is difficult to believe that, when thus given, it can accumulate in sufficient quantity in certain small areas to cause severe erosions. It will be seen, therefore, that the pathogenesis of the gastric lesions of arsenic poisoning must be left without satisfactory explanation for the present.

In cases where a large amount of white arsenic has been given by the mouth, close inspection—especially examination with a magnifying glass—may reveal undissolved particles of the poison. When the examination is made some days after death, yellow spots may sometimes be found in the stomach or large intestine, or in both. That these colorations are due to the sulphid of arsenic has been affirmed by some and denied by others. In several instances the writer has by analysis detected arsenic in these yellow spots. Brown and Davies examined similar stains in the stomach and intestines, and found only traces of arsenic. They conclude that the coloration was due to some decomposition-product of bile-pigment. However, the evidence adduced for this conclusion might be criticised. Frequently the wall of the stomach or intestine is stained through, so that the coloration may be seen on both the mucous and serous surfaces.

Hoffmann has shown that the sulphid of arsenic may be formed in the body as early after death as two days. He points out the fact that knowledge of the possibility of the formation of this compound so soon may be of great importance, since realgar or orpiment may be employed in suicide, but neither would likely be used with murderous intent. His experiments enable him to state positively that the finding of the sulphid in the alimentary canal two days (or longer) after death is no proof that the arsenic was taken in this form.

The mucous membrane may be thickened with cloudy swelling. At certain points the mucous membrane may be stained with blood, and on attempting to wash away these stains it will be found that it has been detached from the subjacent tissue and is also removed. In some instances deep necrotic changes may be observed. Even when macroscopic lesions are not detectable, there is an infiltration of the tissue with round cells, a condition which has been designated by Virchow as *gastro-adenitis arseni-*

calis parenchymatosa. The upper portion of the small intestines may show alterations similar to those observed in the stomach. Multiple ecchymoses may be found along the intestinal tract. The contents of the small intestine are often thin, watery, and similar to the rice-water stools of cholera. The solitary follicles and Peyer's patches are markedly infiltrated. The alterations in the large intestine may be slight or more apparent. Frequently the epithelial layer is removed from areas more or less extensive, and the mucous membrane is infiltrated with white blood-corpuscles. In animals the above-mentioned changes in the alimentary canal may be observed, according to Pistorius, within two or three hours after subcutaneous administration and within forty minutes after intravenous injection.

The changes induced in the liver and kidneys by arsenic are for the most part microscopic. Only in exceptional instances has fatty degeneration progressed so extensively that it can be recognized by the unaided eye. Ziegler and Obolonsky have made a close histologic study of these organs, and the following statements indicate their findings. Fatty change of the liver-cells is never absent, and is characterized by the presence of small drops in the protoplasm. The fatty changes, however, never involve any large portion of the cells. There are exceptions to this statement, and in some cases the change is as marked as it is in phosphorus poisoning. In many instances this is the only detectable alteration. In others there may be cloudy swelling and necrosis of individual cells. The nuclei often stain imperfectly or fail wholly to do so. Granules staining with safranin may be seen in the protoplasm, showing that the nuclei have been broken down. Sometimes individual cells are seen to be shrunken and homogeneous, appearing brown in stained preparations and showing colored granules instead of nuclei.

That the cells involved in some of these changes are still capable of multiplication is shown by the observation of typical karyokinetic figures. It may be remarked in this connection, that, in the examination of the livers of rabbits long under the influence of arsenic, one gets the impression that the number of double nuclear cells is greater than normal. These proliferating cells may be observed in different parts of the acini, and it cannot be said that they have any local relation to the necrotic foci.

Most of the Kupffer cells are filled with fat drops, and in poisoning of short duration fatty changes are often more advanced in these than in the other cells. Fatty changes in the intra-acinous capillaries are seen here and there. These were first observed in animals which had been treated with arsenic for two days, but the best examples were found after from eleven to seventeen days.

As proliferative phenomena, there were observed swelling of the endothelial nuclei, increase of chromatin, and the appearance of typical karyokinetic figures. The proliferating cells are sometimes round; sometimes they put forth processes which cross the lumen and attach themselves to the opposite wall of the capillary.

The periportal connective tissue is often found to be in a state of proliferation, which is indicated partly by the presence of more or less abundant karyokinetic figures, partly by the increase of cellular elements, and by the presence of numerous cells with large nuclei and rich in protoplasm. These changes can be seen in animals which have been only two days under the influence of the poison, but they become more marked after two or three

weeks. However, one must not expect to find them developed to the same degree in all animals.

In the epithelium of the bile-ducts there is a multiplication of the epithelial cells simultaneously with the proliferation of the connective tissue. After poisoning of long duration, there often appears to be a formation of new bile-ducts. However, the number of bile-ducts in the periportal connective tissue in rabbits is normally so great that a positive statement on this point cannot be made.

Changes strictly attributable to an inflammatory condition are not prominent. However, single leukocytes are observed in the proliferating areas, and sometimes the intra-acinous capillaries contain many leukocytes. In point of time or place, the proliferation shows no recognizable dependence upon the degeneration.

In dogs which have been treated for three months with doses of from 0.01 to 0.1 gm., extensive fatty degeneration is observable. Some liver-cells show vacuoles. Furthermore, many endothelial and connective-tissue nuclei are filled with granules, which stain intensely red with safranin. In the kidneys the epithelium of the tubuli recti are fatty to a high degree.

In acute arsenic poisoning, hemorrhagic points may be found not only in the alimentary canal, as has been stated, but also in the muscles, pancreas, the lungs, in serous membranes, and in the endocardium. The presence of ecchymoses in the endocardium of the left ventricle is frequently observed and is regarded by some as pathognomonic of arsenic poisoning.

In chronic arsenic poisoning, fatty changes may be observed not only in the organs mentioned, but also in the muscles, including those of the heart and diaphragm, and in the mesenteric glands.

Antimony.—The pathologic changes induced by preparations of antimony are so similar to those caused by arsenic that no extended statement is necessary. Indeed, the remarks on the pathologic anatomy of antimonial poisoning will be largely confined to the few lesions which are distinguishable from those of arsenic poisoning.

The frequency with which the tartrate of antimony is employed as a mordant has given opportunity for the study of its effects upon the unbroken skin. A pustular eczema is induced, and the suppurative process may extend through the deeper layers of the skin and even involve the subjacent tissue. Moreover, these breaks in the continuity of the cutis expose the tissue to the action of pyogenic germs, and the extension of the lesions may be due to these.

Upon the mucous membrane of the alimentary canal, the action of antimony differs from that of arsenic most notably in the appearance of aphthous patches in the mouth, esophagus, and stomach. Indeed, the local effect of arsenic is less marked than that of antimony. Schmiedeberg accounts for this on the ground that preparations of arsenic are absorbed more readily than those of antimony. It is on account of its marked local irritation of the stomach that antimony, acting reflexly, becomes the powerful emetic that it is.

The lesions produced in other organs by antimony are practically identical with those induced by arsenic.

Phosphorus.—Poisoning with phosphorus is so frequent, and the lesions induced by it are so well marked, that it is a favorite study of pathologists.

In doses of 0.1 gm., phosphorus is poisonous, inducing gastritis accompanied by vomiting and pain. Death may result within a few days, from failure of the heart; but more frequently the primary symptoms subside and are followed by a short period of comfort, when secondary symptoms manifest themselves. Pain reasserts itself; the liver is found to be perceptibly enlarged; icterus is observed; there may be some elevation of temperature; vomiting is renewed; the pulse becomes feeble; and delirium, frequently accompanied by convulsions and terminating in a coma resembling that of uremia, may mark the last stages of the intoxication. Often ecchymoses appear beneath the epidermis, and hemorrhages from the nose, stomach, bowels, and uterus have been noted. As a rule, death occurs in acute poisoning after from five to fifteen days.

Fatty changes are found in the most diverse tissues, such as the epithelium and glands of the stomach and intestines, the liver, kidneys, pancreas, lungs, heart, blood-vessels, and both smooth and striated muscles. Ecchymoses, and occasionally profuse hemorrhages, may be found in different tissues. When the poison has been taken by the mouth, erosions are frequently seen in the stomach and upper intestines, and the mesenteric glands are hyperemic and swollen. Fatty changes in the liver are easily detectable in experimental animals as early as twelve hours after the administration of the poison, and in chronic poisoning many liver-cells will be found to be wholly destroyed. In chronic poisoning, both the heart and the kidney may suffer most extensive fatty changes.

Wegner treated animals with gradually augmented doses of phosphorus, and states his findings substantially as follows: The liver-cells of the periphery are destroyed by fatty changes. In the greater number of the acini the cells are stained with bile, and this is due to the pressure of proliferating tissue on the minute branches of the gall-ducts. Soon an interstitial hepatitis will be found. This invariably leads to atrophy, of which three kinds have been observed. These are (1) a smooth induration of the organ, (2) a lobulated liver with many deformities, (3) a typical granular atrophy, the classic cirrhosis of the liver. In all of these there is chronic icterus. When the last-mentioned form of atrophy exists, it is found to be accompanied by secondary lesions well known in human pathology—venous hyperemia of the mucous membrane of the stomach and intestines and indurative enlargement of the spleen. These animals develop ascites and hydrothorax.

Hemorrhages and ulcerations were found in the stomach. In the animals kept for months under the influence of the poison, the mucous membrane of the stomach was found to be thickened to two or three times the normal condition, indurated, and colored gray or brown. In growing animals, small doses long continued produced sclerotic bone in the endochondral zones, and the periosteal deposition became at the same time thicker. In adult chickens, small doses caused the medullary cavities to fill with bone, and in case of fracture the formation of callus was hastened. When administered in small doses to pregnant animals, phosphorus is believed to increase the formation of bone in the fetus.

In a dog killed after it had been given small doses of phosphorus daily for thirty-six days, Krönig found necrobiotic changes with fatty degeneration in the liver-cells, accompanied by dilatation of the blood-vessels and the gall-ducts. In another animal which died after seventy-nine days, he found a hyaline degeneration in the walls of the blood-vessels and the usually observed changes in the liver-cells. In a third dog killed after one hundred and six days, the changes in the liver-cells were much more pronounced. Many appeared

homogeneous or contained vacuoles and were without nuclei or showed only broken-down nuclei. The lobules contained brownish foci consisting of granules, leukocytes, and disintegrated cells. Swelling and hyaline degeneration of the endothelium of the blood-vessels were noticed. The periportal connective tissue was increased. The blood-corpuscles were believed to have suffered hyaline degeneration and to be deprived of the power of normally performing their physiologic function.

Ziegler and Obolonsky observed, in the early stages of phosphorus intoxication, fatty and other changes in the liver-cells. The nuclei were often found to be broken down, while granules stained with safranin could be seen distributed through the protoplasm. Even after more chronic poisoning, the amount of fat in the liver-cells was often found to be small. The degenerative changes were generally found to occur simultaneously in different parts of the acini, but in some instances they were most marked along the periphery.

The question has arisen as to whether the fat found in the liver and other tissues is formed *in situ* or results from an infiltration. Lebedeff has endeavored to prove that this fat is transported from subcutaneous deposits. He fed dogs for a long time upon foreign fats, such as linseed oil, and, after he supposed that the normal fat of the body had been replaced by that of the food, he poisoned the animals with phosphorus and satisfied himself that the fat found in the liver-cells was of foreign origin. However, there is no proof that the subcutaneous fat was replaced by that of the food. Leo claims that both processes go on. He finds experimentally that, while other parts of the body may lose and the liver gain in fat, the total amount in the body is increased by phosphorus poisoning, and consequently he concludes that there must be some actual production. The location of fatty globules in the liver-cells, in the glands, and in certain muscles, its speedy appearance after the administration of the poison, and the other evidences of cellular degeneration leave little room to doubt that the fat is at least in part formed *in situ*. No proof has, however, been brought, according to Rosenfeld, Taylor, and others, that the fat is formed out of the proteids of the cells.

One of the most interesting lesions of chronic phosphorus poisoning is the necrosis of the bones of the jaws formerly observed frequently among workers in match-factories. This necrosis is due to the action of vapor of phosphorus, and occurs among those who dip the ends of the matches in the phosphorus bath. It begins as a periostitis, most frequently in the inferior maxillary, about a decayed tooth. It is accompanied by salivation and great pain. Extraction of the tooth shows the presence of pus in the alveolus. The suppuration extends into the alveolar processes, destroys the gum, and involves the adjoining teeth, which become loose and fall out. The pus formed gives off a fetid phosphorus odor. The destructive process may not stop with the gum, but may involve the skin; and deep abscess may form in the neck. Early in the process there is an abnormal deposition of osseous tissue; but later this is destroyed, and the old bone forms a sequestrum which must be removed. Amyloid degeneration of the abdominal organs is one of the secondary effects of the long-continued suppuration, and basilar meningitis frequently leads to death. Improved methods in the manufacture of matches and advanced sanitation in the factories have greatly diminished the number of cases of phosphorus necrosis.

Tissue metabolism is much disturbed in poisoning with phosphorus. This cannot be explained on the supposition that any large proportion of the

oxygen needed to carry on normal metabolism is consumed in the oxidation of the phosphorus, because but little oxygen is required to oxidize the small amount of phosphorus which constitutes a fatal dose, and secondly because it has been demonstrated that no appreciable oxidation of phosphorus takes place in the body. Bauer has shown that the amounts of oxygen taken into the blood and of carbonic acid given off are enormously decreased in phosphorus poisoning. According to this observer, not only is fat formed from proteid constituents of the body, but paralactic acid occurs in the blood and urine in abnormal quantity, and much of the nitrogen which normally exists in the form of urea is eliminated in the urine as ammonia. The red blood-corpuscles rapidly decrease in number, and the conversion of hemoglobin into bile-pigment takes place so rapidly that not only is the whole body icteric, but the urine is highly colored with this pigment. That the blood-corpuscles disintegrate more rapidly than their coloring matter can be changed into bile-pigment is shown by the presence of unchanged blood-pigment in the urine. According to the researches of Selmi, unknown poisonous basic substances appear in the renal secretion. These have been designated as phosphorus ptomains. The urine contains ammonia, paralactic acid, albumin, pepton, bile-pigments, bile-acids, hemoglobin, bases containing phosphorus, fat globules, fatty casts, cell detritus, and blood-corpuscles. Whether or not leucin and tyrosin exist preformed in the urine is a question not yet satisfactorily settled. At any rate, these crystalline bodies may be obtained by the usual method of concentrating the urine and extracting with alcohol.

The suggestion that acute yellow atrophy of the liver is a form of phosphorus auto-intoxication resulting from the formation of free phosphorus in the intestines by the reducing action of bacteria on phosphates rests upon no scientific basis.

The Oxygen Compounds of Phosphorus.—Schulz has studied the action of salts containing the oxygen compounds of phosphorus. The hypophosphite of soda is inert. The phosphite of soda is markedly poisonous, having its chief effects on the central nervous system and on the glandular organs of the abdomen. After acute poisoning the mucous membrane of the fundus of the stomach shows large blood-extravasations, while the pylorus is dotted with multiple ecchymoses. In more chronic cases the liver and kidneys show a fatty degeneration. After death from phosphite of soda subcutaneously administered, the intestinal tract is highly inflamed, the glands especially being involved. The mucous membrane is infiltrated with blood and shows numerous hemorrhagic points. The pyrophosphate causes gastric and intestinal hemorrhage, and hemorrhagic spots under the renal capsule have been observed. The metaphosphate also acts as a gastro-intestinal irritant.

Lead.—Lead combines readily with albumin, and some of the lesions found in the alimentary canal after poisoning with this substance may be due in part to this action; but that lead is a poison merely on account of the readiness with which it forms a compound with albumin is not true, because the albuminate of lead and other noncorrosive compounds of this metal are quite as poisonous as the inorganic salts.

In acute lead poisoning, gastritis is generally more or less marked. There may be ulceration. The mucous membrane of the intestines is shrivelled, anemic, and frequently stained grayish brown with the sulphid of lead. In animals, serous effusions under the membranes of the brain and cord have

been observed. Coen found inflammatory infiltrations in the lungs, liver, and kidneys, with cloudy swelling and vacuolization in the epithelium of the stomach, intestines, pancreas, kidney, adrenals, and liver, but no evidence of fatty changes.

Chronic lead poisoning furnishes the pathologist with abundant material for study, inasmuch as the lesions are both decided in degree and extensive in area.

Disturbances in the alimentary canal occur both when the poison enters by the mouth and when administered hypodermically. Indeed, when soluble salts are injected under the skin or intravenously, they are in part eliminated from the circulation into the stomach and intestines. Coloration of the gums is one of the signs of chronic saturnism first looked for by the physician. Massazza observed it in dogs three days after the administration of the poison was begun, but generally it appears much later. This coloration is due to the formation of the sulphid of lead. The gums and often the teeth are stained; sometimes the inside of the lips and cheeks shows flame-like bluish patches. This sign is most marked in persons who neglect cleansing the mouth. Ulceration of the stomach and upper intestines is sometimes found. The peptic glands undergo fatty degeneration and may be obliterated in certain areas. The submucosa is thickened on account of a proliferation in its connective tissue. The solitary and agminated glands of the intestines suffer fatty degeneration or atrophy. Fatty changes may be detected in the muscular walls of the stomach and intestines. There may be contractions in the connective tissue of the walls of the alimentary canal, leading to abnormalities of form and position.

Lead colic with great pain may occur repeatedly in the course of chronic poisoning, and even for months, possibly years, after the introduction of the poison into the body has ceased. This colic is accompanied by contraction of the circular fibers of the intestines. If the contractions are slight and interrupted, there will be diarrhea; but when they are complete and continuous, a most intractable constipation results. Lead colic was formerly believed to be due to an affection of the sympathetic system, especially of the solar plexus; but recently it has been attributed to irritation of motor ganglia in the intestinal walls. Strangury or ischuria may occur along with lead colic. The blood-pressure is decidedly increased during the colicky attack.

After death from an attack of colic in a man who had long suffered from chronic lead poisoning, the writer found the intestines so tightly constricted for a distance of several inches that neither air nor water could be forced through them. However, too much importance must not be attached to this condition, as it may be observed after death from other causes. In chronic lead poisoning experimentally induced in rabbits, the cells of the peptic glands are found to be cloudy and undergoing fatty degeneration, and the signs of venous stasis and ecchymosis are present. There is proliferation of the submucous connective tissue, and sclerosis may be well marked.

It is generally believed that lead is eliminated to some extent by the skin. Cases of chronic poisoning have been reported in which the epidermis has been darkened on the application of dilute solution of sulphid of sodium or after bathing in water impregnated with hydrogen sulphid gas. However, perspiration collected after the administration of pilocarpin in these cases has been found free from lead. Kobert suggests that the poison may be contained in the epidermis in an insoluble form. Lesions of the skin are not constant in this affection, but may occur; the most common form is a pustular erythema. The existence of an *icterus saturninus* has been both affirmed and denied by

good clinicians, which shows that it may occur, but is not constant. In long-continued saturnism the subcutaneous fat disappears, the skin becomes wrinkled, dry, and brown, giving an appearance of old age. Anesthesia is occasionally observed over circumscribed areas, and may be confined to the skin or extend to deeper tissues; it is due to the action of the poison on peripheral sensory nerves and is transitory.

The number of red corpuscles and the amount of hemoglobin are diminished. According to Grawitz, the red blood-corpuscles in lead poisoning often contain basophilic granules, staining with methylene-blue.

The disturbances of vision which occur in chronic saturnism are probably secondary to the effects of the poison on the kidneys. Stood divides them into two classes: the first he considers a neuritis due specifically to the action of lead, and states that it may occur without the co-existence of albuminuria; the second he regards as a retinitis such as may occur with contracted kidney due to other causes. Between and connecting these is hydrops of the sheath of the optic nerve, which may be a consequence either of nephritis with hypertrophy of the left ventricle or of peripheral retrobulbar neuritis. The neuritis generally begins with inflammatory phenomena, easily recognizable with the aid of the ophthalmoscope; but it is often impossible to determine exactly what part of the nerve is most seriously affected. According to Oeller, hyaline deposits in the vessels of the choroid and retina may be found in some cases of lead poisoning.

The minute anatomy of the contracted kidney of chronic lead poisoning has been studied by numerous clinicians and pathologists, but their findings have led to diverse views. In brief, it may be said that some contend that the lesions begin in the blood-vessels. The arteritis, they say, leads to contraction here and there and to occlusion of the lumen of the blood-vessels, while the parenchyma secondarily becomes atrophied and the interstitial connective tissue proliferates more or less. Others hold that lead first injures the secreting elements, and that the affection of the blood-vessels is secondary and in no wise characteristic. Guyler believes that the primary and most important histologic changes are found in the blood-vessels and begin in an endarteritis which leads to obliteration of the capillaries. The process differs from an ordinary arteriosclerosis in the disappearance of muscle-cells with thickening of the middle layer by the growth of fibrous tissue. The endothelium proliferates and contracts the lumen. The walls thicken by the deposition of the granular material, which later becomes homogeneous. Finally complete occlusion results, and the capillaries involved are converted into glistening, compact, homogeneous tissue. He designates the process as "*vasculitis capillaris obliterans*." The deposit in the blood-vessels is a hyaline substance similar to that found in other forms of arteriosclerosis.

The sequelæ to the alterations in the kidney are identical with those which follow contracted kidney due to other causes, and which are described in the section on the kidneys.

Lead arthralgia is not accompanied by any constant or characteristic lesion. In lead gout, uric acid may be deposited in the contracted kidneys and in various joints.

Lead paralysis, although common in chronic poisoning, is not constant. The musculospiral nerve is the first and often the only one involved. So constant is this that paralysis of this nerve or its branches is generally regarded as due to lead, even when inquiry fails to reveal the manner in which the poison has been introduced.

"Drop-wrist" may result from the external application of preparations containing lead, as happens in the use of certain cosmetics, as well as when the poison is taken by the mouth. Atrophy of the muscles usually follows paralysis, but in some instances the atrophy may precede paralysis. Very rarely the deltoid or the biceps is more seriously affected than the muscles of the hand and wrist. The peroneal muscles are sometimes affected in lead paralysis. General paralysis as a result of lead poisoning has been reported. Paralysis of one or both vocal cords is said to be a typical symptom of lead poisoning in horses, and paralysis of the adductors of the larynx has been observed in men. Atypical paralyses are likely to result from the combined action of two or more poisons, as lead and alcohol or lead and syphilis.

Examination of the parts involved in lead paralysis shows changes in the muscles, blood-vessels, and nerves. The alterations in the muscles may be macroscopic. They are much wasted and pale or yellowish. Microscopically certain fibers will be markedly altered, while others are quite normal. The diseased fibers are shrunk and sometimes show an enormous proliferation of nuclei. The position of a fiber may be indicated only by the presence of granular debris and clusters of nuclei. The changes in the vessels are those of arteritis obliterans. Changes in the nerves are most evident in their peripheral terminations, but may extend backward to the trunks, and are those seen in other forms of neuritis.

Lead encephalopathy is a term used to designate a form of chronic lead poisoning accompanied by symptoms referable to disturbances of the brain, as delirium, melancholia, convulsions, and coma. It is a question whether this condition is due to the direct action of the lead on the brain-cortex or results from the general arteriosclerosis and changes in the kidney. Be this as it may, the most exhaustive researches have failed to show either gross or minute lesions in the brain.

Mercury.—Mercurial compounds are generally divided into mercurous and mercuric preparations; the latter are the more poisonous. However, the difference in action is one of degree rather than of kind. While very large doses of calomel may be given without harm, its continued employment is not free from danger, and even metallic mercury in a finely divided state has been known to cause death in at least two instances. The ethyl compounds of mercury are exceedingly poisonous, and two chemists have lost their lives in experimenting with them. Mercuric chlorid owes its corrosive action to the avidity with which it combines with proteids, and all mercury preparations enter the blood in the form of an albuminate. This is also true of the metal itself. When absorbed from a mucous membrane or through the unbroken skin, albuminous compounds are formed. It must not be supposed, however, that the poisonous action of mercury is dependent upon the formation of proteid compounds, or that saturation with albumin renders mercury inert. The albuminate itself is poisonous and may induce stomatitis, salivation, and enteritis.

In acute mercurial poisoning, whatever may have been the method of administration, there will be a brownish or black coloration of the gums and marked inflammation with ecchymoses in the mucous membrane of the alimentary canal. Death may occur within a few minutes from the administration of a very large dose. In such a case the histologic changes are not likely to be prominent; but in the majority of instances death is delayed for two or three days, possibly longer. When a large dose of corrosive sublimate is taken, the effect may resemble that induced by mineral acids. There may be most violent inflammation of the mucous membrane of the mouth, pharynx, and larynx, with consequent edema of the glottis. The

erosions in the stomach and intestines may be extensive and deep, even to perforation. Ulceration of the ileum and a diphtheritic condition of the large intestine, with and without perforation, have been observed. Frequently the mucous membrane, from the mouth to the pylorus, is found diffusely colored. Ludwig reports a case in which the mucous membrane of the esophagus and stomach looked as if it had been cooked. The bronchial tubes are often highly inflamed, and ecchymoses on the endocardium are found; while degeneration of the muscle of the heart has been seen, even when death resulted within two or three days. The marrow of the bones may be highly injected. Ulcers soon form on the gums, and the kidneys and liver show lesions which will be described later. According to Virchow, the anatomic changes in the large intestine cannot be distinguished histologically from those of acute dysentery. Chemically mercury can be detected in the tissues. However, the intestine is not invariably seriously involved, as cases have been reported by competent observers in which no changes or only those of very slight degree could be detected. Indeed, there are rare instances in which very large quantities of corrosive sublimate have passed through the alimentary canal without more harmful effect than a severe purging. The writer knows of a fortunate case of this kind, where a man swallowed a tablet containing seven and one-half grains of corrosive sublimate, mistaking it for quinin. According to Kaufmann, involvement of the intestinal walls depends upon the formation of thrombi in the capillaries, with consequent necrosis, while the diphtheritic condition is ascribed to the action of bacteria. In acute poisoning from administration by the mouth, peritonitis with bloody serous exudate may occur.

The changes in the kidney are most interesting. If a section of this organ be placed under the microscope and treated with dilute sulphuric acid, effervescence takes place and the formation of crystals of gypsum may be seen. This is due to the fact that in mercurial poisoning calcification occurs in the renal epithelium.

In very acute cases the kidneys are hyperemic and frequently show hemorrhagic spots. When the poisoning is less rapid, the condition resembles that of an acute parenchymatous nephritis. On microscopic examination there will be found cloudy swelling and necrosis of the cortical tubules. Fatty changes may or may not exist. Hyaline or granular casts may be found in the tubules, and the interstitial connective tissue may be infiltrated with small cells. Deposits of lime are found in the tubules, most abundantly in the convoluted ones. The question has arisen whether or not this calcification of the kidney can be regarded as pathognomonic of mercurial poisoning. Weichselbaum states that it cannot be so considered, because it is seen in poisoning with other substances, as manganese, bismuth subnitrate, glycerin, etc.; but he adds that the finding of abundant chalky deposits in the convoluted or straight tubules of the cortex should be considered a strong suggestion of mercurial poisoning. The cause of these deposits is another interesting question. The old theory that the lime deposited in the tubules is withdrawn from the bones has been shown to be erroneous. Kaufmann offers his theory of thrombosis in explanation, but it is more rational to explain the calcification by the supposition that the epithelium injured by the mercury is no longer able to eliminate the lime salts of the urine. This, with the diminished secretion of urine, which may lead to anuria, is probably sufficient cause for the formation of the deposits. In

this connection it is interesting to state that the researches of E. Ludwig have shown that the places of predilection for the deposition of mercury are the kidneys, liver, and walls of the large intestines, in the order named.

Muscular tremor is one of the common manifestations of chronic mercurial poisoning. Paralysis of the upper extremities may occur; it is not accompanied by atrophy, and microscopic examination of the nerves shows cloudiness and granulation of the neurilemma without alteration of the axis-cylinder.

The malar necrosis resembles that due to phosphorus. There is much difference of opinion concerning the effect of chronic mercurialism on the bones; since so many of the individuals in whom these lesions have been studied were syphilitic, it is difficult to decide to what extent the bone-lesions should be attributed to this disease or to the effect of the mercury.

Copper.—Metallic copper is not poisonous unless it be taken in finely divided form, when the gastric juice may dissolve it in sufficient quantity to prove injurious. All the salts of copper, however, are poisonous.

In acute poisoning with copper, the mucous membrane of the whole alimentary canal is inflamed and changed in a greater or less degree. Ecchymoses may be found anywhere along the tract. Ulceration may occur in the stomach, small or large intestine, and may proceed to perforation. Patches of green or bluish coloration may be seen here and there. The hemoglobin of the blood is more or less broken down, with the formation of an excess of bile-pigment leading to marked icterus. Unless death occur within twenty-four hours, there may be found fatty changes in the liver and kidney, the latter organ showing also the appearances of acute parenchymatous degeneration. The poison, albumin, casts, blood-pigments, and bile-pigments may be found in the urine.

Zinc.—The chlorid is the only actively corrosive compound, but all the salts are poisonous. The mucous membrane of the alimentary canal, especially that of the stomach, is inflamed and corroded. The corrosive action of zinc chlorid is characterized by the formation of a hard, dry crust which remains in place. The walls of the stomach are hardened and contracted. The kidneys show a parenchymatous degeneration. Albumin and casts are found in the urine. Chronic zinc poisoning among those engaged in smelting has been frequently reported, but it is questionable how much of the ill effect is due to zinc and how much to associated metals, as lead and arsenic.

Aluminum.—Practically alum is the only salt of aluminum from which poisonous effects are likely to result. This is true merely because alum is the only soluble salt of aluminum that is widely used. All salts of aluminum are poisonous when injected subcutaneously or intravenously. The researches of Siem, confirmed by those of Döllken, have demonstrated that the lesions induced by the subcutaneous administration of salts of aluminum are extensive and serious. In animals they found the lesions of "metallic kidney" and fatty changes in the anterior horns of the spinal cord.

Silver Nitrate.—The only preparation of silver from which poisoning has resulted is the nitrate. In acute poisoning with this salt, its caustic action is responsible for the most prominent lesions. The nitrate of silver in strong solution or in the form of lunar caustic produces a more or less deep eschar when brought in contact with tissue. On portions of the body exposed to the light, this eschar soon turns brown or black, while on the mucous membrane it remains white. The eschar consists of the albuminate of silver,

and the change in color on exposure to light is due to reduction of the salt to metallic silver or one of the lower oxids. Postmortem examination after acute poisoning shows only escharotic lesions in the mucous membrane.

Chronic poisoning with silver is known as argyria and is of great interest to pathologists. Since the publication in 1859 of the now classic paper of Frommann, on the pathologic lesions of argyria, much interest has been manifested in this subject. Nitrate of silver was formerly of some repute in the treatment of epilepsy, and many cases of argyria resulted from its employment in this disease. Argyria may result from the long-continued employment of nitrate of silver in any disease. In a case of ulcerative colitis treated at the hospital of the University of Michigan, the colon was washed daily with a solution of silver nitrate (1 dram to 4 pints), and well-marked argyria appeared within eight months. The subject of Frommann's studies had taken about three and one-half ounces of this salt in pill form within about ten months. During the greater part of this time, he took one six-grain pill each day. The face began to show evidences of pigmentation about two months after the treatment was begun. The coloration gradually deepened and extended to other parts of the body. A chronic gastritis developed, accompanied by pain, which at first was intensified only on taking one of the pills, and later by food. There was frequent vomiting, and restriction to liquid food was found to be necessary. It is interesting to note that the patient developed tuberculosis while thus saturated with silver.

The only parts of the skin free from pigmentation were the palms of the hands and the soles of the feet. In the brain the Pacchionian bodies were prominent, the arachnoid showed some cloudiness, and the choroid plexus was grayish blue. Pigment indurations and calcified tubercles were found in the lungs, along with cavities and miliary tubercles. The walls of the left ventricle of the heart were much thickened. The mucous membrane of the stomach was reddened and dotted with small hemorrhagic erosions, while one oval ulcer 7 cm. long and 5 cm. broad occupied the posterior wall midway between the cardia and the pylorus. The floor of this ulcer was uneven, and at one spot it consisted of the pancreas, the stomach being perforated and adherent to this organ. There was a stricture of the pylorus, apparently due to hypertrophy of the muscular and submucous layers.

The mucous membrane of the small intestine was thin, and the intestine itself was contracted. The follicles were filled with black granular deposits. Under the microscope these granules were found to vary much in size and form, but none was crystalline. On treating a thin section containing these granules with a solution of potassium cyanid, they disappeared. Similar granular deposits were found to be abundant in the spleen.

The liver was small, full of blood, and contained cells undergoing fatty changes. Granular deposits were observed in the middle of the acini, apparently surrounding the small veins. On microscopic examination of a cross-section of the small vessels, the lumen was seen to be enclosed by a black ring. The coloration was in part granular and in part diffuse.

The deposits of silver seemed to be most abundant in the kidneys, and it is to these organs that students of argyria have subsequently given most attention. Frommann found that the pyramids were stained dark gray, the color being deepest near the papillæ and becoming lighter toward the cortex. On section of the cortex the glomeruli appeared as black dots. Micro-

scopically they were seen to contain finely granular material which conformed to the shape of the vessels and was quite distinct from the capsule. Some glomeruli were more intensely colored than others. Unchanged Malpighian bodies were found to be few. The same finely granular material observed in the blood-vessels was found deposited on and between the walls of the tubules of the pyramids. Toward the papillæ these deposits were most abundant, becoming less toward the cortex, but not disappearing altogether. On cross-section the tubules appeared, each surrounded by a broad black ring. The walls of the convoluted tubules showed no abnormality except fatty epithelium. These granular deposits dissolved in solutions of potassium cyanid, and became white and opaque on the addition of nitric acid, and again black on subsequent treatment with ammonium sulphid. Other investigators have confirmed the statements of Frommann, but von Kahliden finds the histologic changes in the kidneys to be more marked than others have supposed. It might be conjectured that the individual from whom von Kahliden obtained his material suffered from some co-existent disease to which these lesions might be attributed; but he points out that the distribution of the histologic changes corresponds exactly with the deposits of silver, and moreover he has found a similar condition in a rabbit in which argyria had been induced experimentally. It is highly probable that Frommann and others have been so much interested in the study of the deposits that they have given insufficient attention to the observation of co-existent degenerative changes. The changes observed by von Kahliden may be stated as follows: In the places containing the granular deposits, and only in these, the connective tissue is markedly increased—from six to eight times the normal. Within the hyperplastic regions the straight tubes are much compressed and their epithelium exfoliated. At the same time the hyperplastic tissue undergoes hyaline degeneration, and this is followed by calcification, which involves not only the altered connective tissue, but also the epithelium of the tubules as well.

Riemer supposes that the silver compound is reduced in the intestine, and the finely divided metal is taken up by the blood and lymph and mechanically deposited; but Naunyn has shown that the distribution is wholly different from that which occurs with a finely divided pigment. Loew thinks that silver is reduced in the body only by the living cell, that Riemer is in error when he states that the silver is never found combined with cellular elements or deposited in them, and that a more exact study of the blackened glomeruli shows that the silver is deposited in the endothelial cells surrounding the Malpighian bodies. He also states that the text-book assertion that the epithelium of the glomeruli is impermeable to finely divided particles, founded upon Riemer's studies of argyria, is erroneous.

In the kidney the deposit of silver is always most marked around the afferent vessels of the glomeruli.

Rozahegzi has studied the lesions induced in animals by chronic poisoning with salts of silver. He found the mucous membrane of the trachea and larynx usually hyperemic, sometimes purple red. In the lungs, hyperemia and edema were marked. In many instances there were hepatized areas, and in one a caseous focus. The pulmonary epithelium showed fatty changes, while the connective tissue of the walls of the alveoli showed proliferation. The liver exhibited principally cloudy and fatty changes and consecutive hyperplasia of the interlobular connective tissue. The epithelium

of both the convoluted and the straight tubules of the kidneys was swollen and granular, and the detritus resulting from disintegration filled the lumen. Fatty changes of the epithelium were seldom observed, and then existed only to a slight degree in the convoluted tubules. The striated muscles were soft and pale; the striations were frequently found displaced. The muscle-sheath sometimes contained large drops of fat.

Chromium.—Those compounds in which chromium acts as a base are only feebly poisonous, while those in which it plays the part of an acid are markedly active. Chrome-alum and chromium hydrate, known as Guignet's green, are the best known compounds of the first group. The alum is harmful only in large quantities; and the green, when free from mixture with boric or picric acid, is wholly insoluble and inert. On the other hand, chromic acid and the chromates are actively poisonous, as a dose of one-half grain of the bichromate of potassium may cause unpleasant effects. Chromic acid is a powerful caustic, and all the chromates induce more or less local reaction.

In acute poisoning the vomited matter is green or blue, on account of the reduction of the chromium by organic matter. Either of these colors in vomited material may possibly be due to altered bile-pigment; but when blood and shreds of mucous membrane from the stomach are present in green or blue vomit, the possibility of chromium poisoning should not be forgotten. The stools are watery and stained with blood-pigment. The urine is diminished in amount and contains albumin and casts. The skin may become icteric in a few hours after the administration of a poisonous dose.

The mucous membrane of the mouth in acute poisoning is swollen and sometimes quite detached from the subjacent tissue. The gums are often stained bluish green. The lining of the esophagus may be highly inflamed, while that of the stomach is swollen, detached in places, and ecchymosed; erosion may extend to the deeper tissues. Hyperemia and ecchymosis of both the small and large intestines are generally found. The peritoneum may be inflamed and the cavity may contain a blood-stained serous exudate. The mucous membrane of the bladder may show hemorrhagic spots, and, when death is delayed for a few days, ulceration. The bronchial tubes may be involved in the general inflammatory condition, and effusion into the ventricles of the brain may occur. The blood becomes brownish from the action of the poison on the hemoglobin, and methemoglobin is formed along with the other decomposition-products. The liver-cells speedily undergo fatty changes, but the alterations in this organ in acute chromium poisoning have not been closely investigated. This form of intoxication has been employed by Gergens and by Posner in the study of acute inflammatory processes accompanied by the formation of casts in the kidneys. Animals are treated subcutaneously with from 0.25 to 0.4 gm. of the neutral chromate of potassium dissolved in from 2 to 4 gm. of distilled water. A few hours after the injection the kidneys show no macroscopic changes of importance, but the microscope reveals an interesting condition. The epithelium of the convoluted tubes shows cloudy swelling and ragged borders. The glomeruli are moderately injected and their capsules contain a larger or smaller volume of an exudate which is coagulable on the application of heat. Various elements are detected in the contents of the tubules, especially a large number of round cells enclosed in a fine network, apparently due to the coagulation of some albuminous fluid. This is believed to illustrate the formation of casts in these tubules. Posner concludes from

his studies that fibrinous masses may be formed in the tubules at a time when the epithelial cells, although not in a normal condition, are certainly not absolutely necrotic.

Instances of chronic poisoning have been observed after the employment of a chromate in the treatment of disease, as in the Guntz cure for syphilis; J. Wm. White has recorded a fatal result from the application of chromic acid to a large number of condylomas about the buttocks and vulva. But poisoning is most common among workmen engaged in the industrial use of chromium compounds. Injurious effects may follow the external application and the inhalation of these preparations, as well as from ingestion through the alimentary canal. When taken by the mouth, contracted kidney with its sequelæ is one of the most prominent and disastrous effects. Externally it leads to ulceration of the hands, arms, inside of the thighs, etc. Furuncle, eczema, impetigo, and pseudopsoriasis are given by Kobert as frequently observed accompaniments of ulceration of the skin. The drum of the ear, more frequently the septum of the nose, may be perforated. An ulcerative conjunctivitis has been observed, and the inhalation of the poison in the form of dust leads to bronchitis. Deep ulcers often form in the pharynx.

Nickel and Cobalt.—Soluble salts of nickel and cobalt are poisonous. The most constant lesions are blood-extravasations in the stomach, intestines, and in the epicardium and endocardium. In acute cases there are no changes in the blood, while in chronic poisoning both the corpuscles and the percentage of hemoglobin are diminished. Small coagula are frequently observed in the heart.

Barium Chlorid.—Practically the only salt of barium ever used for its poisonous effect is the chlorid. In the intensity of its action this substance equals white arsenic. Kobert finds records of twenty-six cases of poisoning with barium salts, and of these about half terminated fatally. Some years ago the writer saw a woman who had taken with suicidal intent about twenty grains of barium chlorid. The early recognition of the nature of the poison, some of which was found in the room, prevented serious results.

Barium chlorid acts as an irritant, but is most harmful in its effects upon the nerve-centers. The nausea and diarrhea which appear are in part the result of its action on the ganglia of the intestine. It has a digitalis-like effect on the heart. The heart beats very slowly and so violently that its movements may be seen and even heard at some distance. As a consequence of this enormous increase in blood-pressure, ruptures and hemorrhages in diverse organs may occur.

At autopsy no changes are observable, at least not constantly, in the mouth or esophagus; but the stomach is reddened and ecchymoses may be extensive in the intestines. As has already been indicated, small hemorrhages may be found in the lungs, in the walls of the heart, in the cord and brain, and in their meninges. When administered hypodermically or intravenously, barium chlorid is eliminated by the stomach and intestines and causes local irritation in these organs. In animals experimentally poisoned with this substance, thrombi caused by the insoluble sulphate have been observed, and granular deposits of the same salt have been found in the kidneys. These findings have not, however, been reported in man.

Potassium Chlorate.—The reckless manner in which this salt was used a few years ago, and is still employed by some, caused much harm. Potassium chlorate should never be administered internally, and as a gargle

in various affections of the throat there is no justification for its employment, and it should be supplanted by more scientific and less dangerous treatment.

Potassium chlorate owes its poisonous properties to the fact that it converts the hemoglobin of the red blood-corpuscle into methemoglobin. The readiness with which this action goes on depends on several conditions. The higher the temperature, the more rapidly does the poisonous action manifest itself; therefore it is especially harmful when administered in fevers, exactly the condition in which it has been most extensively prescribed. Again, decreased alkalinity of the blood favors the poisonous action of potassium chlorate. The dyspnea which often accompanies the throat-affections in which this salt has been so widely used decreases the alkalinity of the blood by interfering with the elimination of carbonic acid gas. The simultaneous administration of dilute preparations of the mineral acids has a similar action. Thirdly, the density of the blood influences the action. By the addition of such indifferent substances as sodium chlorid, glucose, and serum albumin, the intensity of the effect is magnified.

With relatively small doses the transformation of hemoglobin begins within the corpuscle; but with larger quantities the equilibrium between the formed elements and the plasma is destroyed, and the corpuscles go to pieces and the transformation continues in solution. The debris of the disintegrated corpuscles accumulates in various organs, interrupting their functions; and at the same time, the oxygen-carrying power of the blood being diminished, disturbances of metabolism necessarily result.

In the most acute cases, which have generally resulted from mistaking the chlorate for purgative salts and swallowing large quantities in a fasting condition, death results within a few hours. Vomiting, diarrhea, dyspnea, marked cyanosis, and weakness of the heart's action are the most prominent symptoms.

In acute cases the only constant change found after death is that resulting from the action of the poison on the red corpuscles; the blood is thick and brown.

In less acute cases, such as have been observed from its excessive use in throat-affections, the detritus resulting from the disintegration of the red corpuscles will be found collected in such organs as the kidney, spleen, liver, and bone-marrow, which are generally swollen. The skin is icteric, and grayish-violet spots may be seen. Often the corpuscles which are not broken appear as though they contained nuclei; some are quite pale. The bone-marrow is brown and filled with disintegrated corpuscles. Both the straight and convoluted tubules of the kidney are filled with cylinders made up of cellular detritus.

The chlorates of sodium, magnesium, and calcium are poisonous, but are less so than the potassium salt.

The Mineral Acids.—The local effects of the mineral acids are dependent upon the concentration rather than upon the amount. When applied to the skin or brought in contact with mucous membrane, the concentrated mineral acids destroy the tissues. When thus applied during life, the area of contact is soon surrounded by one of inflammation. When applied after death, the tissue is also destroyed, but there is no evidence of consequent inflammation. When a concentrated mineral acid is swallowed, the mouth and stomach generally show the most marked effects. The esophagus may escape with only slight irritation. When the quantity swallowed is not large, the acid passes down the esophagus and along the smaller curvature of

the stomach toward the pylorus. The most noticeable changes will be found along this line, and the frequency of pyloric ulceration and stenosis after poisoning with the strong mineral acids is thus explained. When the lesions in the stomach are not sufficient to cause speedy death, the gastric juice may digest the portions of the walls over which the mucous membrane has been destroyed, and thus lead to perforation.

The poisonous effects of the mineral acids are not wholly confined to the local destruction of tissue; they may cause death by diminishing the alkalinity of the blood. The life of herbivorous animals is speedily jeopardized by increasing the amount of acid in the body; while the carnivorous animals and man will bear large quantities of acid, provided it be administered sufficiently diluted. This difference is explained by the fact that carnivorous animals may, in case of need, supply a large amount of ammonia, which will neutralize the acid. Indeed, the greater part or all of the nitrogen generally eliminated by man in the form of urea may appear in the urine in the form of ammonia combined with some acid. The need of the body's ability to furnish ammonia to neutralize acid is seen in some forms of diabetes, in which the quantity of oxybutyric acid formed within the organism is large.

Sulphuric Acid.—The ease with which this acid can be obtained under the name of the oil of vitriol, and the popular knowledge of its action, have made it an agent frequently employed in suicide, especially in former times. Moreover, it is altogether probable that the extensive destructive action of the acid has had a fascination for the diseased mind intent on suicide. Quite naturally its employment in homicide has been very rare. The acid is sometimes thrown into the face, and it has been injected into the vagina and rectum.

When concentrated sulphuric acid is brought in contact with the skin, there is severe pain and the spot turns first white and then brown; after a few minutes the adjacent skin becomes red and swollen. The epidermis is soon destroyed, and the destructive action may extend to the deeper tissues. In the case of a man who attempted to swallow a large quantity of the acid, spasm of the pharynx prevented his doing so, and the fluid ran from the mouth over the chin and neck. The destructive action on the tissue was so great that the resulting scar bound the chin down upon the breast, and a plastic operation was necessary. When the area of skin destroyed by contact with the acid is great, intestinal ulceration develops, as it does after extensive burns, and the individual falls into a somnolent condition, leading to coma and death. This is undoubtedly due, as it is in extensive burns, to alterations in the blood.

When the acid is thrown into the eyes, conjunctivitis and keratitis result, followed by glaucoma, often leading to blindness.

In case of death from swallowing the acid, brownish marks are frequently seen extending from the corners of the mouth, over the lower jaw, and down upon the neck. The lips are excoriated or uniformly parched brown. The mucous membrane of the mouth and tongue is covered with a white or brown layer of altered tissue. The acid actually burns the tissues and destroys their histologic elements. In the stomach similar changes are found, but the destructive action is deeper than in the mouth. Frequently the wall is pierced through and the effects of the acid may be seen on adjacent organs; perforation has been reported in about one-third of the cases. Black spots consisting of decomposed blood-pigment may be

seen in the stomach, and, in case of perforation, in the peritoneal cavity. The alterations in the intestines resemble those found in the stomach, but are less intense and gradually grow less marked in the lower portions. Parenchymatous inflammation develops in the liver and kidneys.

Chronic poisoning with dilute sulphuric acid is rare, but according to Kobert it occurs in France from two causes. He states that in the lowest drinking-places this acid is added to brandy to make it "bite," and that it is also added to wine to "improve" it. According to Weiske, chronic poisoning in animals is accompanied by the withdrawal of lime salts from all the bones except the vertebrae and the skull.

Kobert states that chronic poisoning with the acid sulphates of lime and potassium, which are formed in wine on the addition of dilute sulphuric acid for the purpose of precipitating the gypsum, may occur. He also thinks that the acid sulphate of lime is an important factor in death from inanition in herbivorous animals. The sulphuric acid which results from the oxidation of the sulphur of the proteid tissue is insufficiently neutralized. According to the same authority, the substance sold as the neutral sulphate of potassium is frequently employed in England and France, and sometimes causes death. Section shows the stomach and intestines inflamed. This effect is attributed to the presence of the acid sulphate or to impurities, as zinc and copper.

Nitric Acid.—This acid is largely used in various manufactures, and medical literature contains the records of about 400 cases of poisoning, mostly accidental. Nitric acid colors the skin yellow, and this becomes orange on the addition of ammonia. The coloration of proteid material by nitric acid is known as the xanthoproteic reaction.

When the acid is taken in solution of 20 per cent., or more dilute, the local effects are not prominent. When the concentration reaches 33 per cent., or is greater, the local effects are similar to those of sulphuric acid, excepting the yellow coloration. In the intestines the mucous membrane is stained gray or grayish white, and this is regarded by Lesser as important in distinguishing between poisoning with this acid and with chromates. The stomach may be perforated and the abdomen distended with gas. The kidneys show an acute parenchymatous nephritis.

According to Bellin, nitric acid in daily doses of from 10 drops to 15 gm. is used in Russia as an abortifacient. Chronic poisoning results from the treatment, and is characterized by tremor, insomnia, marked anemia, gastric catarrh, and diminished secretion of urine. In two cases section has shown fatty changes of the heart, nutmeg liver, enlargement of the spleen, nephritis, and effusion beneath the meninges of the brain. It is possible that some of these effects may have been due to arsenic in the acid.

Hydrochloric Acid.—Lewin finds reports of twenty-six cases of poisoning by this acid; one was a homicide. Stricture of the esophagus is frequent, but perforation of the stomach is rare, although it may occur. Kobert states that purulent mediastinitis and exudative pleuritis result. Fatty changes of the liver and nephritis have been observed. A chronic auto-intoxication from hypersecretion of this acid in the stomach is regarded as possible, but on this point we have no positive knowledge.

Lehmann found that an atmosphere containing one part or more per thousand of the vapor of hydrochloric acid causes in animals a flow of tears, conjunctivitis, and cloudy swelling of the cornea. The duration of exposure necessary to induce these effects varies with the ability of the animal to

protect the eye completely by closure of the lids. The tears were observed to be milky, and microscopic examination revealed the presence of fat globules, believed to come from the Meibomian glands. The mucous membrane of the nose is inflamed, and some days after the exposure a purulent nasal catarrh may set in and lead to a dry necrosis or a moist gangrene involving the septum and the alæ and causing rather extensive destruction. This effect is supposed to be due to the local action of the gas upon the blood-supply of these parts. In some animals the salivary glands are greatly stimulated. In animals dying during the experiment or killed soon after exposure, the trachea was pale with a few ecchymoses. The bronchial tubes contained a thin, frothy secretion. There was uniformly an emphysematous condition, and pneumonic changes were observable in animals that survived the exposure twenty-four hours and longer. In all the guinea-pigs exposed to an atmosphere containing one part per thousand or more of the gas, hemorrhagic spots were found in the mucous membrane of the stomach. Slight ecchymoses were observable in Peyer's patches in two animals—a rabbit and a guinea-pig.

Chlorin and Bromin.—Researches of Lehmann on poisonous gases convinced him that chlorin and bromin are both qualitatively and quantitatively alike in their effects upon the animal organism, while they differ widely from the vapor of hydrochloric acid. The effects upon the eyes and upon the mucous membrane of the nose and mouth are much less marked than those of the acid, and necrosis of the septum and alæ of the nose did not occur in any instance. The effects of these gases are most evident in the lungs. Even when the atmosphere contained only 0.01 : 1000 of either of these gases, and after an exposure of six and one-half hours, there developed after twenty-four hours a mucopurulent bronchitis with pneumonic foci and marginal emphysema. Edema of the lungs was much more constant and pronounced than in poisoning with either ammonia or hydrochloric acid vapor. Especially marked was the macroscopic filling of the perivascular lymph-spaces about the larger pulmonary vessels. When the percentage of the gas was increased, a typical croupous membrane formed, and in some instances was continuous from the larynx to the finest bronchi. When the amount of gas reached 0.3 : 1000 and the exposure continued for one hour or longer, the membrane was invariably found. Great dyspnea and stupor were marked symptoms.

Hydrogen Sulphid.—The frequency with which man is exposed to the action of this gas, one of the products of many putrefactive bacteria, renders a study of its poisonous effects of great interest. Hydrogen sulphid, when given off from decomposing matter, is generally mixed with other gaseous products of putrefaction, as CO_2 , CO , and NH_3 ; and the effects may be exceedingly variable, according to the relative amount of each of these present. Moreover, an atmosphere largely contaminated with these gases is generally poor in oxygen, and this deficiency has its own ill effects. Accidental poisoning with the pure gas occasionally occurs in laboratories.

The injurious effects of hydrogen sulphid are probably underestimated by those who have neither tested its action nor acquainted themselves with the literature of the subject. The writer has repeatedly observed its effects in sterilized bacterial cultures when its presence was hardly perceptible to the sense of smell and when silver or lead paper placed over the test-tube blackened very slowly. Boutny and Descout found that 1 c.m. of very

filthy water yielded 140 c.c. of H_2S on being agitated, and 46 c.c. more on being boiled. From this they conclude that 1 c.m. of the water would furnish enough of this gas to render 28 c.m. of air fatally poisonous. That both men and animals may acquire marked immunity to this poison is undoubtedly true. Dupuytren and Thénard found an air containing 0.66 : 1000 of this gas poisonous for birds, 1.25 : 1000 poisonous for dogs, and 4 : 1000 poisonous for horses. Biefel and Polek found that a rabbit died after 75 minutes' exposure to an atmosphere containing 0.59 : 1000 of H_2S , and another rabbit died after an exposure of two hours to air containing only 0.37 : 1000.

Lehmann has made some valuable experiments upon the poisonous effects of this gas. He employed a Pettenkofer-Voit respiration apparatus. All the animals showed signs of local irritation after prolonged exposure to air containing only 0.13 : 1000. A narcotic effect was evidenced by the position taken by the animals. Paralysis gradually developed and death resulted from failure of the respiration. In cats, death was preceded by a restless sopor. Under doses of 0.72 : 1000 there was great dyspnea accompanied by convulsions, sometimes with opisthotonos. In all of these cases death was not due to paralysis of the nerve-centers solely, but in part to simultaneous changes in the lungs. At first the respiration became slow, then with increasing dyspnea it became very rapid. Section showed edema of the lungs in all animals exposed for some hours to the action of the gas. The lungs were voluminous, diffusely dark red, and showed punctiform blood-extravasations. The fluid of the edematous lungs was very abundant, stained with blood, and often ran from the mouth before death. Marginal emphysema was seldom absent, and in some instances was highly marked. Together with the edema, there was frequently a pleuritic effusion.

Edema of the lungs is not seen in the apoplectiform poisoning with hydrogen sulphid which occurs when animals are exposed to an atmosphere containing a large amount of the gas.

Death from sewer-gas containing a large amount of hydrogen sulphid is often instantaneous and leaves no constant changes except that the blood is fluid and dark. Generally all the chambers of the heart contain fluid blood.

Hydrocyanic Acid.—Compounds yielding hydrocyanic acid under certain conditions are widely distributed in the vegetable world. Poisoning, however, is very rarely due to these substances. The official dilute hydrocyanic acid, containing 2 per cent. of the acid, is quite properly but little employed. Most cases of poisoning are accidental and come from the cyanids so largely used in the arts, rarely from the dilute acid.

Hydrocyanic acid, either free or combined with potassium, is one of the speedily fatal poisons. The writer has seen animals die within thirty seconds from the effects of large doses. It rapidly diffuses throughout the body and appears in the excretions. Its odor is easily detectable in the exhaled air. In making postmortem examination when this poison is suspected, the odor given off from the stomach and other cavities of the body is of great significance, and the pathologist should bear in mind that the inhalation of the gas from the dead body is not altogether free from danger. At least one case is recorded in which serious poisoning occurred in this way. There is no proof that hydrocyanic acid is decomposed in the body, and in nonfatal cases the whole of the poison is believed to be eliminated unchanged.

In poisoning in man, it is customary to speak of three stages. The first is characterized by dizziness, headache, and precordial pain; the second stage, known as the asthmatic, is marked by great difficulty of respiration; and the third, known as the convulsive, appears when the now unconscious victim is seized with violent convulsions. However, when a large amount is given, there are only a few spasmodic attempts at respiration, and life is extinct.

The dead body usually shows areas of bright-red coloration. According to Kobert, these spots are due to the presence of cyanomethemoglobin, a compound having a characteristic spectrum resembling that of reduced hemoglobin, but not identical therewith. On cutting into the tissues, however, the blood of the subcutaneous structures and of the viscera is found to be dark red, unless the quantity of the poison taken has been very large; in which case the blood throughout the body may be bright red. Whether the blood be light or dark, most of it will be fluid, and it has only slight tendency to coagulate.

The mucous membrane of the stomach is generally injected: sometimes uniformly, and in other instances only over limited areas. The right side of the heart is generally filled with blood, while the left is empty. The lungs are sometimes edematous, and there may be effusions into the ventricles of the brain. The urine is likely to contain blood and sugar, along with an unknown reducing substance. The characteristic odor can often be recognized in the urine.

Cyanogen gas and the iodid of cyanogen are poisonous, inducing effects similar to those resulting from hydrocyanic acid. Sulphocyanid of potassium is generally regarded as inert; but in very large doses it resembles hydrocyanic acid in its action on the blood. This is of special interest on account of the fact that it is a normal constituent of the saliva and of the urine.

Carbon Monoxid.—This substance, which is the most poisonous constituent of so-called coal-gas, has caused many deaths; and without doubt it is responsible for many fatalities attributed to other causes. It has been largely employed for suicidal purposes, and many instances of accidental poisoning with it are known. In the five years from 1848 to 1852, in France 1401 persons intentionally killed themselves by inhaling this gas. Illuminating gas made from coal contains from 5 to 10 per cent. of CO, while that made from wood may contain as much as 60 per cent. Water-gas, now so largely used for illuminating purposes, contains about 30 per cent. Organic dust, falling upon heated stoves, burns with the evolution of appreciable quantities of CO. There has been some difference in the statements concerning the amount of this gas necessary to render harmful the inhalation of air containing it. The most exact experiments place it at about 0.02 per cent.

The most poisonous effect of CO results from the readiness with which it combines with hemoglobin and from the stability of the compound thus formed. The affinity of CO for hemoglobin is about two hundred times greater than that of oxygen. From this it will be seen that, even when the inhaled air contains only traces of CO, this substance is retained and accumulates in the blood. It should be distinctly understood that, even in fatal poisoning with this gas, the greater part of the hemoglobin remains in combination with oxygen. The writer recently saw a report of a case of poisoning with CO, in which the statement was made that there was no oxyhemoglobin in the blood; and yet this was not a fatal case, and the patient lived

for months and continues to live, so says the paper, without oxyhemoglobin. Such a statement as this is absurd. Death results when the respiratory capacity of the blood is reduced from 20 to 30 per cent. Saturation of the hemoglobin of the blood with CO during life is impossible.

In recovery from slight poisoning with this gas, it is slowly dissociated from the hemoglobin and exhaled. It is not oxidized to carbonic oxid gas. The corpuscles the hemoglobin of which is combined with CO retain their normal form and are not immediately disintegrated, but are destroyed more quickly in the liver than are the corpuscles the hemoglobin of which is in a normal condition. The lethal quantity of CO for a man weighing 70 kilograms is computed by Dresser at 0.8 gm., from his experiments on rabbits. The whole of the gas inhaled is not held by the hemoglobin; some of it is dissolved in the plasma, and some of it penetrates the tissues, and may, according to Fehling, pass from the mother to the fetus.

CO hemoglobin gives off no oxygen to the tissues, and the symptoms induced are partly those of asphyxiation. Blood containing this gas is of a cherry-red color, and this may be observed in some instances many days after death. The spectrum of CO hemoglobin shows two dark bands between the lines D and E, and is similar to the spectra of oxyhemoglobin and hemochromogen. However, these spectra are not identical, and with all of them in view they can be easily distinguished. The oxyhemoglobin spectrum lies farthest to the left, that of hemochromogen farthest to the right, extending slightly beyond E, while that of CO hemoglobin lies between. Furthermore, the lines are not so widely separated as in the oxyhemoglobin spectrum. Again, the addition of a reducing agent to normal blood speedily changes its spectrum, while this does not happen when one-fourth or more of the coloring matter is combined with CO.

CO, besides its indirect effect on the tissues by interrupting the oxygen-carrying power of the blood, is a direct poison and capable of inducing marked destructive changes. Primarily the heart beats slowly and violently. Rupture of blood-vessels may occur during this stage. Secondly the heart beats rapidly and feebly. This is the period of vasomotor paralysis; and as a result of this condition, bright-red areas may appear on the surface. When not seen until after death, they are generally mistaken for postmortem effusions. However, they may occur in those who ultimately recover. At first there may be abnormal motility, and possibly violent convulsions; later there may be extensive paralysis. In about 70 per cent. of the cases of poisoning with this gas, the urine contains a reducing substance, which in some instances is sugar, in others glycuronic acid. A test for reducing bodies in the urine may serve as an aid to diagnosis in doubtful cases. Albumin also is present in about 20 per cent., and lactic acid appears in severe poisoning.

The degenerations that may result from chronic poisoning with CO are numerous and extensive. The marked and persistent anemia so frequently observed is due in part to the rapid destruction of CO-bearing corpuscles by the liver, and in part to the nephritis that comes from the elimination of the decomposition-products. In dogs chronically poisoned with this gas, the epithelium of the convoluted tubules undergoes necrotic changes and may be stripped off altogether. The enormous increase in nitrogenous metabolism with muscular degeneration reminds one of phosphorus poisoning.

Musso has reported five interesting cases of chronic poisoning; one of them showed progressive weakness, both physically and mentally. There was incoordination of movement, including speech, with repeated epileptiform attacks. Of the five, two slowly recovered, and three passed into a condition of typical paralytic dementia and died. The blood-vessels in various organs were found to have undergone fatty and hyaline degeneration. Koren has reported other cases, in one of which section showed dilatation of the heart consequent upon advanced fatty degeneration of the muscle, serous effusion in the pericardium and the pleural cavities, and an enlarged spleen.

In acute poisoning, the color of the blood is considered pathognomonic. The skin is likely to be stained over limited areas; and the soft tissues, the muscles and viscera, are rose-red. According to Kobert, CO hemoglobin has been detected in the body eighteen months after death. The corpuscles retain their form some time after death, and the arteries are generally full of blood. There are ecchymoses in the meninges and capillary hemorrhages in the brain. Pneumonic changes are frequently observed in the lungs, and fatty changes in the kidney, liver, and heart. Ziemssen found a diphtheric-like exudate on the gums, in the trachea, and in the colon and rectum. Gangrene of the muscles of the neck has been reported. Deep bedsores have been known to form in a very short time.

The Caustic Alkalies.—Locally the caustic alkalies destroy tissue in much the same way as the strong mineral acids. However, there is this difference: the eschar formed by the acids is hard and dry, while that formed by the alkalies is soft and gelatinous. It is the difference between syntonin and alkaline albuminate. Scar-formation and resulting contractions are similar after acids and after alkalies. The penetration of the tissue is also deep, and perforation of the walls of the alimentary canal may occur. Stricture of the esophagus is a frequent result of the local action of the caustic alkalies. The effect of the subcutaneous injection of strong alkalies is influenced to an important degree by the injured part remaining free from bacterial infection or by its becoming infected. In the former instance the necrosis is confined to the muscles, while the blood-vessels remain unaffected and the nutrition of the part continues. The writer saw an example of this a few years ago, when a physician injected strong ammonia in different parts of the body in a case of morphin poisoning. The necrosis of the muscular tissues was extensive around the point of each injection, but the blood-vessels remained intact. On the other hand, when infection happens, the blood-vessels may be closed by thrombi and the nutrition of the part is prevented. The local action of strong alkalies upon nerves results in degenerative changes which are histologically similar to those due to section of the nerve.

Caustic Potash and Soda; Caustic Lye.—After swallowing any of these in concentrated solution, the mucous membrane of the mouth and pharynx is white and swollen, with dissolved or necrotized patches. The mucosa of the stomach is macerated and corroded, exposing the reddened subjacent tissue. There may be perforation. The intestines are highly inflamed. If death be delayed, ulcerations occur along the alimentary canal, and later contractions with stricture of the esophagus may result. Even when the esophagus is not closed, the contractions in the walls of the stomach may be sufficient to reduce materially the size, alter the form, and destroy the function of this organ.

Although the carbonates both of potash and soda have a local caustic action, poisoning is practically limited to the potash compound. This is due to the more markedly depressant action of potash, especially on the vasomotor center and the heart.

Ammonia.—This poison may be inhaled in the form of gas, or it may be taken into the stomach, dissolved in water or in alcohol. In gaseous form it causes inflammation of the mucous membrane of the nose, mouth, pharynx, larynx, and bronchi. The conjunctiva may also be much inflamed, and prolonged exposure may lead to ophthalmia. The inhalation of ammonia leads to free salivation, and this may be accompanied by nausea and vomiting. A pseudodiphtheric membrane may form in the larynx and lead to great dyspnea. Lehmann found that animals compelled to breathe air containing from two to three parts per thousand of ammonia-gas showed salivation, inflammation of the conjunctiva, dyspnea, and convulsions terminating in death. On section he found edema of the glottis, hemorrhage, and, when death was delayed, purulent bronchitis. Microscopic examination showed some of the alveoli quite normal, others collapsed, and still others emphysematous. The lung-tissue was infiltrated with numerous leukocytes, and, in the hemorrhagic foci, unchanged red corpuscles were seldom seen; but leukocytes were abundant and surrounded by pale-red masses and swollen epithelial cells. In rabbits that died during the experiment, the most constant and prominent lesions consisted of hemorrhagic tracheitis and laryngitis. The tracheal epithelium was extensively destroyed and the cells robbed of their cilia. In the case of one animal that had survived an exposure of four and one-half hours to a $5\frac{1}{2}$:1000 atmosphere, but died during a second experiment, Lehmann found purulent fibrinous pleuritis and pericarditis. He attributes the pleuropericarditis to the action of bacteria which had found their way into the blood through lesions caused by the gas.

When a solution of ammonia is swallowed, the mucous membrane of the mouth and pharynx is swollen, reddened, and destroyed in patches. The stomach contains bloody fluid, and the walls are inflamed and may be perforated. The blood may be dark or light red, but it shows no spectroscopic changes. Fatty degeneration and ecchymoses may be found in the liver, and a glomerulonephritis may be established. The changes in the lungs resemble those observed after inhalation of the gas, but are generally less pronounced.

Caustic Lime.—The lesions induced by caustic lime have not been closely studied, and only general statements can be made. A child that fell into a lime-pit is said to have died almost instantaneously. Others, who ate apples cooked by being placed in unslaked lime, showed evidences of local irritation and had convulsions. An old man is said to have rubbed caustic lime and green soap over his entire body; the epidermis turned brown and was destroyed. Suppurating ulcers may result from external application, and parenchymatous nephritis may develop later. When taken internally, caustic lime corrodes the mucous membrane of the stomach and intestines, the blood becomes thick and cherry-red in color, and the meninges of the brain are hyperemic. When drawn into the lungs, the epiglottis is swollen and the mucous membrane of the trachea and bronchi is corroded and becomes grayish white.

VEGETABLE AND SYNTHETIC POISONS.

The Organic Acids.—**Oxalic Acid.**—This substance in strong solution is an escharotic, but it is poisonous apart from its action as a caustic, inasmuch as the neutral oxalate of potassium may cause death. The insol-

ble oxalates, such as those of lime and magnesium, are inert. It is now an established fact that the presence of soluble salts of lime in the blood is essential to the phenomenon of coagulation; and both free oxalic acid and the soluble oxalates, by precipitating the lime, prevent coagulation and so alter the composition of the blood that disastrous results follow. At the same time, normal metabolism is interrupted and sugar appears in the urine.

There are those who believe that the condition known as oxaluria, characterized by the continued deposition of crystals of the oxalate of lime in the urine, is a form of chronic poisoning with this acid, which may be introduced from without, especially in certain vegetable foods, or be generated within the body as a result of imperfect oxidation, and that this chronic poisoning is frequently followed by diabetes. However, our knowledge concerning the significance of a continued deposit of oxalate of lime is yet too indefinite to permit the expression of any positive statements.

In acute poisoning with the acid, the mucous membrane of the mouth, esophagus, and duodenum is grayish white and more or less corroded. The mucous membrane of the stomach may escape injury, but generally it is swollen; and close inspection will reveal numerous pin-point hemorrhagic spots. Microscopic examination shows crystals of calcium oxalate in the folds of the mucous membrane.* In many instances there is a bloody diarrhea, and octohedral crystals may be found in the discharges. Various crystalline forms—octohedra, dumbbells, plates, and whetstones—may be found in the uriniferous tubules, and on the line between the cortex and medulla these crystals may accumulate in such quantity that the concretions formed may be seen by the unaided eye. The statement formerly made that only dumbbell forms are developed in the kidneys, while the octohedra first crystallize in the bladder, has not been substantiated by more thorough investigation. Convulsions and motor paralysis are among the possible symptoms in acute poisoning with oxalic acid, but the writer has not been able to find any record of study of the central nervous system.

Acetic Acid.—Kobert states that after death there is extensive infiltration of blood under the skin, giving a violet coloration. The tongue and esophagus are white or brownish from the local irritation. The stomach contains a brownish fluid, while the walls are violet or brownish, possibly black. The mucous membrane of the small intestine is thickened and brownish red, while the peritoneum is violet gray.

Carbolic Acid.—In 1882 Kobert collected 169 cases of acute poisoning with carbolic acid, and in 1893 he added about 50 more to the list. In a large number of suicides that recently occurred in Philadelphia and New York, carbolic acid was employed as the agent. Chemically, carbolic acid is, of course, not an acid.

A certain quantity of phenol combines with sulphates and glycuronic acid in the body, and these conjugated acids are eliminated by the kidneys. It is generally stated that phenol is not poisonous until the amount is greater than that which can be taken up by the above-mentioned bodies. In accord with this belief, the clinician at one time was guided in his administration of phenol and kresol by the amount of inorganic sulphate in the urine; and so long as barium chlorid produced in this excretion a precipitate insoluble in hydrochloric acid, it was believed that the danger-line had not been reached. There is undoubtedly some truth in this, inasmuch as the conjugated phenol is much less poisonous than the free body; but it is by no means certain that the conjugated acids are wholly free from deleterious effects, especially on the kidneys.

Concentrated carbolic acid, when applied to the unbroken skin, gives it at first a white, frozen appearance, followed by necrosis. A 5 per cent. solution benumbs the surface, and after long exposure may destroy the cutis and may even cause gangrene. Even a 1 per cent. solution may form an eschar on a mucous membrane. Whatever be the mode of administration, the kidney shows a condition of acute inflammation in this form of poisoning. The urine becomes dark, containing casts and albumin.

Salicylic Acid.—While salicylic intoxication lasting for some days after the discontinuance of this remedy is not infrequently observed, the acid is generally regarded as devoid of any permanently injurious effects. This belief is warranted by the records of medical literature; and yet salicylic acid is capable of doing injury, and in its employment some precaution is desirable. Hesselbach found that when this acid was administered to rabbits by the mouth, in doses of 1.087 gm. per kilo. of body-weight, it caused death without any special symptoms. Section showed ulceration and partial necrosis of the mucosa of the stomach and marked edema of the whole wall. Hypodermic injection of 1.6 gm. per kilo. caused death, the autopsy revealing marked hyperemia of the kidneys, especially of the parenchyma, also of the liver and of the brain. Microscopic examination of the kidney showed hemorrhagic foci in the interstitial tissue and in the tubules. Epithelial changes were found in certain areas, while others seemed normal. Indeed, in some of the tubules, every cell seemed to be altered. The cell contour was often indistinct, the nuclei sometimes protruded, and the lumen was filled with detritus. In many straight tubules the detritus contained numerous blood-corpuscles. Hesselbach believes that the characteristic effect of salicylic acid on the kidneys is to be found in the hemorrhagic condition and not in the epithelial changes. Hemoglobinuria has been reported as a result of salicylic acid intoxication.

Salol.—This substance, which consists of about 40 per cent. of phenol and about 60 per cent. of salicylic acid, and which splits up into these constituents in the body, is generally believed to be free from poisonous properties. However, this cannot be true, if the dissociation actually occurs; and that this does happen, sometimes completely, there can be no doubt. Carbolic acid intoxication has been observed after the administration of excessive quantities of salol. The odor of this drug was plainly perceptible in all the viscera, especially in the brain. The lower intestines were hyperemic and the stomach the seat of catarrhal inflammation. Microscopic examination showed an accumulation of cellular elements in the renal cortex. Most of the glomeruli were abnormal, and many of them were surrounded by a cellular infiltration. The epithelial cells of the convoluted tubules were in a state of cloudy swelling, and some showed fatty degeneration. The contour of the cells was indistinct, and in many the nuclei could not be discerned. The lumen of the convoluted tubules, without exception, was filled with débris. On treating fresh preparations with osmic acid, there appeared in the cortex numerous dark masses with their long diameters in the radial direction of the parenchyma. They consisted of decomposition-products of epithelial cells undergoing fatty changes, and some of them contained large needles of fat. While the masses of detritus in the convoluted tubules were formless and less numerous, in the straight tubules they were cylindric. Cross-section showed that these cylindric masses consisted of a more homogeneous center, surrounded by large masses of cell nuclei. In a few the

periphery contained red blood-corpuscles, some of which were normal, while others were crenated.

Hesselbach concludes from experiments upon animals that poisoning with salol results from the carbolic rather than from the salicylic acid. This would be the reasonable presumption, since phenol is much more poisonous than salicylic acid.

Picric Acid.—Adler reports a case in which the administration of a 1 gm. dose of picrate of potash led to the following condition: There was severe pain in the stomach and bowels; yellow material was vomited, and a diarrhea with ruby-red stools set in. The phalangeal joints of the fingers of both hands were extended, while the metacarpophalangeal joints were closed. The urine was red, acid, and contained neither albumin nor bile-pigments. A blood-count showed the red corpuscles greatly decreased and the white increased. In other cases of poisoning with this substance, erythema has been noted. There may be transient anuria, and in other instances the urine may be albuminous. In animals experimentally poisoned, Rymza found both the central and the peripheral nerves colored. In the blood, along with broken corpuscles, there may be found red granules, partly free and partly in the white corpuscles, consisting of picramic acid.

Ergot.—At the present time there is no certainty concerning the nature of the active principle or principles of ergot. Kobert has obtained two poisons, sphacelinic acid and cornutin,¹ but not in a state of chemical purity. To the first he attributes the gangrenous changes of ergotism; while the other, he believes, induces the convulsive form that is so pronounced in certain epidemics. More recently Jacobi has obtained a chemically pure body to which he has given the name sphacelotoxin, and which he believes to be the active principle of Kobert's sphacelinic acid. However, the chemistry of ergot remains largely undetermined.

Chronic ergotism manifests itself in two forms: (1) convulsive or spasmodic ergotism, and (2) gangrenous ergotism.

The convulsive form usually begins with gastro-intestinal and vasomotor disturbances. Loss of appetite, nausea, vomiting, diarrhea, cyanosis, formication, muscular weakness, and feebleness of the heart's action are the symptoms. After these have continued for a variable time, symptoms more distinctly nervous occur. Specks are seen floating before the eyes, ringing noises are heard, and irritation of the skin becomes constant. Mental perception becomes dull, and an epileptic condition with the usual hebétude appears. Convulsive seizures become frequent. The flexors overcome the extensors; the hands are bent on the wrists, and the fingers are partly closed. Permanent contractions result. The tendon reflex is soon lost, and the condition resembles that of tabes dorsalis. There may be stupor and acute dementia or melancholia.

In gangrenous ergotism an erysipelatous redness spreads over the toes and fingers, and gangrene sets in. One or more phalanges of the toes or fingers, the feet or the hands, the legs or the arms, may become necrotic and fall off. The external genitals may be involved in these necrotic changes, and gangrenous areas may appear on the skin of any part of the body or in the intestinal mucous membrane.

Grünfeld fed animals with sphacelinic acid. In cocks, gangrene soon appeared in the comb, then in the wattles, tongue, wings, and crop. Hogs lost their ears, and horses and cows their tails, ears, and hoofs. When applied locally in concentrated form, sphacelinic acid caused gangrene of the tissue with which it was in contact.

Grigorjeff submitted animals to chronic poisoning with ergot, and found the following conditions: In the central nervous system the most important changes were localized in the posterior columns (especially those of Burdach) of the cord, extending throughout these and showing the characteristics of a recent myelitis. The alterations consisted of vascular hyperemia, dilatation

¹ Since Kobert's ergotinic acid is inert when given by the mouth, although markedly toxic when administered subcutaneously or intravenously, it cannot be concerned in the causation of epidemic ergotism.

of the perivascular spaces, cell-infiltration often found in colonies, edema of the supporting tissue, and degeneration of the nerve-fibers. In the perivascular spaces, granular cells were frequently found. The degeneration of the nerve-fibers was rendered evident by swelling and granulation of the axis-cylinder and partial disintegration of the myelin sheath. The endothelium of the capillaries was fatty. The other parts of the white and the gray matter of the cord, also the brain, displayed the appearance of passive hyperemia with edema of the neuroglia. In all regions of the cord and the brain cortex there were observed circumscribed collections of blood-corpuscles here and there in the vicinity of the blood-vessels. In a few animals some of the ganglion-cells of the anterior horns of the cord were somewhat swollen and granular. In all there were degenerative changes in the fibers of the posterior roots.

Of other organs, the liver and the kidneys were most markedly affected. In these the changes involved not only the special secreting cells, but the vessels also, and were of an atrophic and degenerative character. In some animals only a few cells relatively were altered, and the changes were not marked; while in others the involved areas were more extensive and the process more advanced. In all the affected animals the cells of the parenchyma of the liver and kidney showed granular degeneration, with less frequent destruction of the nuclei. Fatty changes of the epithelial cells of the kidneys were observed in localized areas. Where the granular degeneration was advanced, it was accompanied by vacuolization of the cell-protoplasm and chromatolysis of the nuclei. The degeneration in the kidney affected principally the convoluted tubules. Hand in hand with the degenerative changes, desquamation of epithelium and the formation of granular casts in the lumen occurred. In the vessels of the liver and kidney, which were distended with blood, degenerative cellular changes were limited to the capillaries, the endothelial cells of which were granular and fatty; rarely the nuclei were destroyed. There was desquamation of the endothelial cells, and the resulting detritus formed finely granular masses. This led to irregular distention of the vessels. Drops of fat were observed in the capillaries, and these were sometimes so massed as to fill the lumen. Sometimes blood-extravasations were found in the capsules of Bowman and in the tubules. Small aggregations of granulation-cells were observed in the interstitial connective tissue in one animal. Along with the above-mentioned degenerative changes in the parenchymatous cells of the liver and kidney, regenerative processes were observed, as shown by the presence of karyokinesis. This was seen more frequently in the endothelial than in the parenchymatous cells. The configuration varied from the normal, inasmuch as the chromatin segments were irregularly divided. Many cells showed both karyokinetic and fatty changes at the same time.

In all the animals, changes were found in the alimentary canal. These were of a catarrhal nature and generally localized in the lower portion of the ileum. In some cases, circumscribed blood-extravasations were observed in the vicinity of the vessels in the mucous membrane.

The changes in the lungs consisted in part of hyperemia and hemorrhages, and in part of involvement of the capillaries. The tissue in the vicinity of the extravasations showed inflammatory phenomena, such as swelling and desquamation of the alveolar epithelium and infiltration of the septa with lymphoid cells. In some of the animals, inflammatory processes

were observed in the bronchioles. The endothelial cells of the capillaries showed changes similar to those observed in the liver and kidney. Fatty emboli were also seen in some capillaries. Very rarely was mitosis observed here.

The heart muscles were atrophied, the transverse striation was lost, and some of the fibers were granular. There was hyperemia, and the endothelial cells of some of the capillaries showed cloudy swelling, granular and fatty changes.

The voluntary muscles and the spleen showed no changes other than hyperemia and atrophy.

In the combs of cocks the alterations were due to occlusion of the blood-vessels with agglutinated red corpuscles and hyaline thrombi. As results of this condition there were edema of the supporting tissue, with emigration of leukocytes from the occluded vessels, and gradual but complete necrosis of the portion deprived of blood-supply. A finely granular pigment was found in the supporting tissue, which probably has its origin in the blood-coloring matter.

The white corpuscles of the blood were increased, while the red were diminished. In cocks the hepatic capillaries were sometimes found containing red corpuscles which had lost their nuclei and were agglutinated into homogeneous masses. Hemosiderin granules were found in some of the capillaries, both in the white corpuscles and in the endothelial cells.

Winogradow studied the pathologic histology of chronic ergotism in the epidemic of 1889 in Russia. The chief changes consisted of hyaline degeneration of the walls of the capillaries, occlusion of the lumen partly with blood-coagula and partly with hyaline masses, and coagulation-necrosis of the parenchymatous elements with proliferation of connective tissue. In the spleen he found necrosis of the Malpighian bodies, and in the kidneys deposits of smooth, glistening masses in Bowman's capsules, with secondary compression of the glomeruli, leading to their complete obliteration.

Morphin.—Although opium contains a large number of alkaloids, morphin is its most active principle and the only one that needs consideration in an article on intoxications. According to Clautrian, morphin and narcotin are the only alkaloids that exist preformed in the plant, the others resulting from fermentative processes in the juice of the poppy during the drying.

Binz thinks that the action of morphin, as well as that of chloroform, is due to a cloudy change or slight coagulation in the substance of the brain. That the chief effect is on the central nervous system must be admitted, but at the same time it must be confessed that neither the histologist nor the chemist has been able to explain in any satisfactory way the mode of action of this poison. Indeed, there is no consensus of opinion concerning its effect upon the circulation in the brain. The most trustworthy experiments indicate, however, that in morphin narcosis the cortex of the brain, at least, is anemic.

A small part of the morphin administered is eliminated in the urine, while the greater part passes out through the bowels. This is true, whether it has been taken by the mouth, hypodermically, or intravenously. This fact is of practical importance for two reasons. It explains why so small a portion of the drug can be recovered from the urine, and it shows the importance of washing out the stomach in morphin poisoning, even when it has been administered subcutaneously. In cases of poisoning, morphin, oxydimorphin, lactic acid, albumin, sugar, and other reducing substances

may be found in the urine. Morphin may also be eliminated in the secretion of the mammary glands, and nurslings have been poisoned in this way. In acute poisoning, death results from failure of respiration and progressive edema of the lungs. This is due to paralysis of the medulla oblongata.

The autopsy findings are not constant nor characteristic. Indeed, cases of unquestionable morphin poisoning are recorded in which the most careful search has failed to reveal any abnormality. Usually, however, the meninges are congested and the cavities of the brain contain an abnormal quantity of cerebrospinal fluid. The lungs are congested and edematous. The blood is dark and fluid, and the bladder is frequently distended. Rarely the abdominal viscera are greatly engorged and ecchymoses are found in the mucous membrane of the stomach. The pupils may be contracted, but no great reliance can be placed on this condition, as they are sometimes quite dilated.

On section after chronic poisoning, the skin is found to be cirrhotic, the muscles atrophied, and the viscera anemic. The brain is edematous; and in animals experimentally poisoned, degenerative changes have been found in the posterior columns of the cord.

Chloral Hydrate.—Locally applied, chloral is a strong irritant; and, when taken in an unsuitable vehicle, it may cause inflammation, hemorrhage, and destruction of the mucous membrane of the esophagus and stomach. Desquamation of the epidermis has been known to follow single doses, and the so-called chloral rash is not infrequently observed. In those chronically addicted to the use of this narcotic, the gums are frequently swollen, the tongue may be blistered, and pustules may form in the skin. In rare instances ulcers form at the base of the nails, and the hair falls out.

Bornträger has collected the literature of forty-four cases of chloral poisoning, and from his studies the following statements concerning the post-mortem findings are chiefly gleaned: Chloral is slightly antiseptic, and it is said that postmortem rigor is somewhat delayed after poisoning with it. However, this is not marked and there may be many exceptions to the rule. Rigor is marked, and it is believed from some animal experiments that chloral coagulates myosin. However, since these experiments were made upon frogs, and since the amount of the poison employed was relatively large compared with the minimum or even the average fatal dose in man, too much must not be inferred from results thus obtained. Subcutaneous effusions of fluid blood are common and are identical with those seen after fatal chloroform anesthesia. The pupils are dilated moderately, sometimes widely. The blood is generally fluid, although this is not so constantly the case as after chloroform. The condition of the heart is variable, with dilatation in the majority of instances. In chronic chloralism, microscopic examination of the muscle of the heart demonstrates the existence of fatty changes. The lungs are hyperemic, sometimes edematous, and marginal emphysema has been observed. The abdominal viscera are engorged with blood, and hemorrhagic spots may be found. The occurrence of ulceration in the stomach has already been mentioned. The meninges are hyperemic, and the brain itself may be either congested or anemic. The urine is sometimes clear and pale, at other times colored with blood.

Sulfonal.—About fifteen cases of chronic poisoning with this drug have been reported. The most constant symptoms consist of the vomiting of a greenish mucus, pain in the abdomen, general weakness, and death from paralysis of the heart. Petechial and pustular eruptions were observed in some cases. The urine contains various coloring matters—hemoglobin, methemoglobin, hematoporphyrin, and bile-pigment. It may or may not contain albumin. According to the researches of W. J. Smith, sulfonal is eliminated for the greater part in the form of ethylsulphonic acid. I have not been able to find any record of the findings at autopsy.

Chloroform.—That chloroform is a cellular poison when used in excess is demonstrated by its frequent application in vapor form for the purpose of killing bacteria, when it is desired to alter the protoplasm of these cells as little as possible. Locally it irritates, stimulates, and then paralyzes. It arrests the ameboid movements of leukocytes and of other low forms of animal life. It coagulates protoplasm; but we can hardly accept the theory of Binz, that its narcotic effects are due to a slight and transient coagulation of the protoplasm of the nerve-cells. The lecithin of nervous tissue is believed to absorb chloroform. It forms a chemical compound with hemoglobin, according to Schmiedeberg, and the corpuscles are capable of taking up large quantities of it. However, under its prolonged action the corpuscles break down. Formed elements in the blood are not essential to the narcotic action of chloroform, because frogs the blood of which has been replaced by saline solution may be anesthetized with it. It benumbs both the gray and the white matter of the brain, and diminishes blood-pressure. The manner in which it kills, whether through paralysis of respiration or of circulation, has been a matter of considerable discussion and experimentation and cannot be dwelt upon here.

The condition of the body after death from chloroform is a matter of both scientific and practical interest. Some have placed much stress upon the intensity and continuance of rigor; but the studies of Bornträger have shown that rigor after death from chloroform is very variable, both in time and in degree. Postmortem subcutaneous effusions are common on account of the fluid condition of the blood, but are not characteristic in appearance. Drops of chloroform on the face may leave significant marks, and the direct effects of the vapor on the eyes may be recognized by redness of the conjunctivæ and edema of the lids. The pupils are generally moderately dilated, but this condition exists in death from many other causes.

The frequency with which air-bubbles are found in the blood after death from chloroform has been the subject of some discussion. As early as 1848, Virchow observed air in the blood after chloroform poisoning. Since that time others have confirmed this observation, and some have gone so far as to claim that air in the blood, except under other explainable conditions, is characteristic of chloroform poisoning. On the other hand, Kappeler has claimed that gas is not found in the blood after chloroform more frequently than after death from other causes. Binz thinks that in the heavy breathing of anesthesia, accompanied as it frequently is by vomiting, by an accumulation of mucus in the throat, and by the unfavorable position often taken by the tongue, air may be forced through the unbroken walls of the air-cells and into the blood. Ewald and Kobert support this view. In this connection Bornträger calls attention to a case in which marked emphysema of the tissues of the neck resulted from the forced respiration employed in morphin poisoning. In 34 out of 41 cases Senator reports the heart shrivelled, flabby, and with its cavities empty at the time when the other muscles of the body were in rigor. Casper regarded this condition as characteristic and designated it as the "chloroform heart," but others do not consider it pathognomonic. However, in a collective investigation of deaths from chloroform, Bornträger finds the above-mentioned condition of the heart to be very frequent. Sometimes all the cavities are empty, sometimes the ventricles are empty while the auricles are filled with fluid blood, and again only one ventricle may be empty. W. Koch found the left heart

generally empty, while the right heart and the veins were full. In 53 cases which Kappeler reports, the right heart contained much blood in 16, all the cavities were full in 6, and all empty in 7. It will be seen that there is no constancy in this condition. No characteristic change has been observed in the lungs. Edema and hyperemia are the most frequent abnormalities. According to Bornträger, subpleural effusion is also common. The mucous membrane of the bronchi is sometimes normal, while in other instances it shows the characteristics of asphyxiation, redness, and hemorrhagic spots. Most of the abdominal organs are congested. The portal vein and the inferior cava are full of blood. Hemorrhages are frequently found, especially in the stomach, spleen, and kidneys. Initial parenchymatous degeneration is observed in various organs when death does not occur until after five or six hours. In dogs subjected to prolonged anesthesia, Strassmann found fatty changes in the heart and liver. The meninges and sinuses of the brain are rich in blood. In 24 cases, according to Bornträger, the brain was reported to be hyperemic and edematous in 8, pale in 6, while in others nothing is stated concerning the condition of this organ.

Alcohol.—The excessive use of alcoholic beverages leads to pathologic changes in most of the tissues of the body. The ill effects of such drinks are frequently attributed to adulterations; but with possibly some few exceptions, the most deadly constituent of alcoholic beverages is the alcohol itself. In its effect on man, amylic alcohol differs from ethylic only in degree and not in kind. The former is the more poisonous, but the pathologic lesions induced are the same in kind, whether the beverage contains a fraction per cent. of amylic alcohol or contains only ethylic.

Alcohol has both a local and a systemic action. The local effect depends upon the concentration, while the systemic is more dependent upon the absolute amount taken and is quite independent of the extent of dilution. Strong alcohol irritates, inflames, and, if the concentration be great enough, may corrode tissue. It absorbs water and destroys the vitality of the cell.

The proportion of alcohol in the blood in the most profound narcosis of drunkenness is considerably less than 1 per cent., but no one knows to what extent it may accumulate in various organs. It is eliminated from the lungs and through the kidneys, but the greater part of it is consumed in the body, the amount eliminated unchanged being only about 5 per cent. of that taken. However, this is subject to considerable variation according to the individual and his condition at the time.

The pathology of alcoholic intoxication can be studied in the living inebriate, in his body after death, and too frequently in his children.

Some of the pathologic conditions that are more or less prominent during life are the following: *Acne rosacea* often prominently obtrudes itself. There is a tendency to the formation of pustules and furuncles, in some instances resulting probably from penetration of the diseased cutis by the pyrogenic germs so constantly present on the surface. Catarrhal conditions, although not confined to alcoholics, are very common among them. The mucous membrane of the nose, pharynx, Eustachian tubes, and stomach is frequently involved. Atheromatous degeneration of the blood-vessels, hypertrophy and dilatation of the heart, and venous stasis are often easily recognizable. Changes in the liver and kidneys cause dropsical accumulations. Changes in the nervous system are indicated by tremor, paralysis, anesthesia, melancholia, and dementia.

When death results from a single debauch in a person not previously a hard drinker, pathologic lesions are not marked. Hyperemia of the brain is the most constant condition. When the alcohol has been taken in con-

centrated form, there may be a high-grade inflammation of the mucous membrane of the alimentary canal, with multiple ecchymoses. There may be edema of the lungs. The odor of alcohol is perceptible in all the viscera and in the muscles.

The findings after death from chronic alcoholism are subject to considerable variation within certain limits. This is doubtless due to the fact that in most instances the use of the poison has been continued through years, during which time the different individuals have lived under widely varying concurrent conditions. In general, the macroscopic changes are as follows: The mucous membrane of the stomach is hyperemic, and the organ contains an excess of thick, tenacious mucus. Ulceration may be present. Changes in the intestines are usually not marked, although there may be some thickening of the membrane and possibly edema.

Alcohol is regarded as the most frequent cause of cirrhosis of the liver, and any one of the forms of this affection may be found in chronic alcoholics.

Frequently a cirrhotic condition is found in the kidneys; but this is by no means constant, and there are those of wide experience who deny that structural changes in this organ are found more frequently in alcoholics than in others. Formad believed that the "pig-backed" kidney was characteristic of chronic alcoholism. The lungs are not the seat of any constant or uniform lesion. The muscle of the heart often appears unusually yellowish and contains an excess of fat. The dura and pia are frequently hyperemic, and the brain may be edematous.

The microscopic pathology of alcoholism has been studied both in man and in the lower animals. Fatty changes are most frequently observed. These are most marked in the liver and the brain, and this is supposed to indicate that the alcohol accumulates in these organs. Both the liver-cells and the so-called cells of Kupffer are involved. The entire protoplasm of the cells may be filled with drops or globules of fat, of variable size. The fatty changes are not uniform, at least in degree, throughout the organ, but are most marked about the portal veins, in the periphery of the lobules, and decrease toward the center. The intensity of the fatty changes varies with the length of time during which the poisoning has continued, and in animals it is increased by the addition of amylic alcohol to the spirit. In some instances the epithelial cells of the gall-ducts contain globules of fat. The nerve-cells of the brain also show fatty changes. The extent to which fatty changes are found in these cells is very variable. In the milder cases the globules are seen only in the periphery, while in more advanced stages the entire cell-protoplasm may be fatty in the highest degree. The nuclei of these cells stain imperfectly, and in some instances seem to be quite disintegrated; the nerve-cell processes are also profoundly altered (Berkley). The walls of the cerebral vessels may contain fat deposited in the connective tissue of the adventitia and in the endothelial cells. Localized fatty changes of the epithelial cells of the convoluted tubules of the kidney may be observed, but the changes are not so extensive as they are in the liver.

In the stomach, the existence of a true glandular gastritis is confirmed by the microscope. The peptic glands are found to be fatty and even necrotic, the chief cells being more extensively involved than the parietal. The spleen and lymphatic glands are infiltrated with corpuscles containing fat.

There is also a granular parenchymatous degeneration in various organs. The nerve-cells of the brain often show this condition to a marked degree,

with vacuolization. This granular degeneration may be marked in the liver; and, like the fatty, it is most marked in the immediate vicinity of branches of the portal vein, where the poison acts in the most concentrated form. Here whitish spots may be seen, and the cells within these areas may exist in a condition of more or less marked coagulation-necrosis. The increase in the connective tissue is easily recognizable.

Lymph-stasis is observable in different organs, especially in the stomach, liver, and brain. Whether this is due to the feebleness of the circulation of the blood on account of the condition of the heart or to nervous disturbances is an undetermined question. The perivascular spaces of the hepatic capillaries may be greatly distended. In the stomach and intestines the submucosa may be very edematous.

Experiments upon animals seem to indicate that the liver-cells may, on the discontinuance of the use of the poison, recover even after marked fatty changes have taken place.

Some Rare Vegetable Poisons.—Abrin and Ricin.—These interesting poisons have attracted much attention on account of their resemblance to bacterial toxins and the venoms of serpents. They are albuminous substances, and in their action bear some resemblance to ferments. Abrin is contained in the jequirity bean, while ricin is the poisonous constituent of the castor bean. They have not been obtained in a state of chemical purity, and were believed by their discoverer, Kobert, to be identical until Ehrlich showed that an animal rendered immune to one is still susceptible to the action of the other. Kobert thinks that their poisonous effects are due to the coagulation of the blood. Not only do they cause the natural blood to coagulate, but, if one of them be added to blood from which all the fibrin has been removed, a new coagulation results, or at least a precipitate forms. This precipitate, according to Kobert, is very similar to, but not identical with, fibrin. Both the corpuscles and the serum obtained from defibrinated blood coagulate on the addition of abrin or ricin. If the corpuscles be repeatedly washed in a centrifuge, and even if all the coloring matter be removed, the stroma shaken in water with abrin or ricin still coagulates.

When administered by the mouth, these substances are much less poisonous than when administered hypodermically. This, which is known to be true of certain venoms also, is explained by supposing that a portion is digested and thus deprived of its poisonous properties. That which is absorbed coagulates the blood in the vessels in the walls of the intestines as soon as it reaches it, a small thrombus is formed, and ulceration results from self-digestion. This is the explanation of the action of these substances, as taught by Kobert. He claims that they are not local irritants, and that all the lesions resulting from poisoning with them are due to their power of coagulating the blood.

The pathology of toxalbumin intoxication as seen in the effects of ricin and abrin has been carefully studied by Flexner, who lays special stress on the occurrence of focal necroses.

Werhovsky has made a valuable contribution to the pathologic anatomy of abrin poisoning. He finds most marked macroscopic changes in the intestines. The peritoneal cavity contains more or less serous fluid. Both the parietal and the visceral layers of the peritoneum are injected, and the large and small intestines contain liquid colored with blood. The mucous membrane of the stomach and intestine is covered with a grayish-white coating; Peyer's patches and the peritoneal lymph-glands are enlarged. The liver and kidneys are swollen and filled with blood. The pericardium

contains a bloody transudate and shows hemorrhagic spots, and both ventricles are greatly dilated and filled with partially coagulated blood. The spleen is enlarged and the lungs are edematous.

Microscopically changes are found to be rather extensive in various organs, but those in the heart and in the digestive organs are believed to be the most significant. The microscopic appearance of the walls of the heart seems to be most characteristic. A transverse section of the fibers shows dark and light spots. The dark cells consist of unchanged muscle-fibers, while the light ones are fibers infiltrated with a light-colored fluid. This dropsical condition of the fibers of the muscles of the heart is believed to be the most unique and characteristic finding. Here and there may be observed swollen fibers, the protoplasm of which is uniformly permeated with drops of fat. All the microscopic findings are believed to be due to a venous stasis. This explanation also suffices for the minute hemorrhagic areas in the lungs, liver, spleen, stomach, intestine, and kidney. Degenerative and inflammatory processes are not prominent.

Werhovsky believes that the cause of death in abrin poisoning is to be found in the above-described changes in the heart. They consist of a characteristic dropsical degeneration in which the involved cells swell to twice their normal size. Simultaneously there may be fatty changes.

Phallin.—This is a poisonous albuminous substance, a so-called toxalbumin, found in different varieties of the fungus *Amanita*. According to Kobert, poisoning with this fungus is not rare in Germany and in the Baltic provinces of Russia. About 75 per cent. of the cases terminate fatally. This fungus is mistaken for edible mushrooms. Kobert states that the poisonous action of phallin is due to coagulation of the blood and solution of the corpuscles. Section shows multiple hemorrhages, especially in the liver and intestinal mucous membrane, also subpleural and intraperitoneal. There is inflammation of the stomach, with partial gangrene and destruction of the glands. There are fatty changes in the liver, heart, tongue, and diaphragm. The urine is brownish and albuminous. The meninges are hyperemic.

If a half-milligram of phallin for each kilogram of body-weight be injected intravenously in a dog, cat, or rabbit, and some blood be drawn from the animal half an hour later, the serum which forms will be reddish. If urine be passed about this time, it will be brownish. Later hemoglobin, methemoglobin, and bile-pigments may be found in the urine. There is also a colored substance which appears to be intermediate between hemoglobin and bile-pigment and closely resembles hematin. After death the uriniferous tubules may contain blood-detritus.

Helvellic Acid.—This is the active constituent of the fungus *Lorchel* (*Helvella*), and disappears when the fungus is dried. The symptoms are similar to those induced by phallin. Section reveals dissolved hemoglobin in the cavities of the body. The kidneys are swollen and the tubules contain hemoglobin in crystals and in small round masses, the so-called "blood-drops" of Bostroem. The spleen contains much hemoglobin. Multiple hemorrhages and fatty changes are observed in the liver.

Saponin Bodies.—About 150 plants belonging to 30 families contain saponin substances. Kobert states that no other poison is found so widely distributed in the vegetable world. The aqueous solutions of the saponins lather like soap. When inhaled they induce sneezing, and on being injected subcutaneously they give rise to aseptic suppuration. They act upon the red blood-corpuscles in much the same way as phallin and helvellic acid act. A few instances of poisoning from bread containing corn-cockle have been reported, due to the presence of a saponin body. Lehmann states that bread containing from three to five grams of corn-cockle is harmful.

As was shown by Przybysaewski in 1876, saponin locally applied dilates the blood-vessels, causes stasis, and alters the corpuscles. This may be demonstrated on the web of a frog's foot. The web is properly placed under the microscope, and the position

of the body is so arranged that stasis will not result therefrom. Then the tissue is pencilled with a 10 per cent. solution of saponin. There is a short period of contraction of the capillaries, then they slightly dilate, and the circulation in the part becomes slow. After ten minutes there is complete stasis, at first in the capillaries, later in the small arteries and veins. The white corpuscles cling to the walls, and thus narrow the lumen and lead to complete arrest of the flow. At the same time the heart continues to beat normally; the stasis is thus the result of the local condition. The red corpuscles become pale and their nuclei show more distinctly. Some of the white corpuscles pass through the walls of the vessels and may be seen on the outside singly and in groups.

The effect of saponin on the red corpuscles can be shown by placing a drop of blood and a drop of 10 per cent. solution of saponin side by side on a glass slide and watching the effects as the two fluids come in contact. If the attention be fixed upon a single corpuscle, it will be seen to swell, the central depression disappears, the color fades, fissures appear along the border, and finally there remains only a small granular body.

When a solution of saponin is injected into a muscle, changes take place and lead to the disappearance of the transverse striation, and finally the tissue loses all its structural appearance.

Phloridzin.—This substance is of interest because it induces a diabetic condition in animals. It is a glucosid and is obtained from the cortex of the roots of certain fruit-trees, such as the apple and cherry. According to the studies of Trambusti and Nesti, the chief lesions induced by this substance are found in the kidneys. The convoluted tubules were found to be constantly altered, the change consisting of necrosis of the epithelial elements, with all the characteristics of Weigert's coagulation-necrosis. The lesions varied in degree in different areas. In the initial stages the cells were found swollen and granular, while the nuclei stained well. In more advanced stages the cells had lost their normal form, and the nuclei failed to stain. Still later only detritus remained, with some chromatin granules. Some of the tubules were filled with this debris. The conclusion from these studies is, that, in experimental phloridzin diabetes in the dog, anatomic alterations in the kidney identical with those observed in true diabetes are found.

The glycosuria following its administration is attributed to the loss of power on the part of the kidney to retain the sugar in the blood.

Nitrobenzol.—The employment of various nitro-compounds in the arts has led to frequent poisoning with the same. However, as the pathology of these poisons has not been closely studied, but little information on this subject can be given at the present time. In man, after poisoning with nitrobenzol, the entire surface and the visible mucous membranes have a lead-gray appearance, but the body after death shows nothing characteristic. Rigor mortis is said to be unusually marked, but this is so variable that no great importance can be attached to it. The odor of the poison is usually perceptible in all the viscera. The stomach and the small intestines are congested and may show numerous ecchymoses. Minute blood-extravasations may also be found in the pleura and in the pericardium. The blood is fluid and dark. When diluted with water and examined spectroscopically, it shows the so-called Filehne's nitrobenzol spectrum. The lines of this spectrum resemble those of acid hematin, but lie slightly to the right. Microscopic examination shows the detritus of broken corpuscles. A peculiar brown pigment is formed in the blood, and to this the above-mentioned spectrum is supposed to be due. This pigment is also found in the urine. In experiments on animals, Rohl found the epithelium of the convoluted tubules stained with this pigment. The kidneys at the same time showed epithelial desquamation with granular cloudiness of the cells. The pigment

could not be found in Henle's loops or in the straight tubes. The brain and its membrane were hyperemic.

Schroder and Strassmann have reported cases of poisoning with metadinitrobenzol and have studied the effects of the same poison on animals. Their work is, however, not complete, and leaves us still in need of more exact information. They report that the mucous membrane of the mouth and throat seems to be covered with a fine yellow powder, which cannot be washed away. The skin is a dirty yellowish brown, the sclera yellow, and the lips blue. The urine is clear and dark brown. The stomach contains colored mucus, and the intestinal follicles are swollen. Microscopic examination of the viscera showed nothing of importance. Fatty changes in the liver have been observed after poisoning with orthodinitrophenol.

Nitroglycerin.—After death from this poison, section shows inflammation and fine hemorrhages in the mucous membrane of the stomach and intestines. The brain is congested, and bloody serum may be found in the cavities. No minute study of the lesions induced by this substance has been made.

Amyl Nitrite.—H. C. Wood discovered the fact that amyl nitrite has a destructive action on the blood-corpuscles, and subsequent studies have shown that methemoglobin is formed. In animals experimentally poisoned with amyl nitrite, section shows a congested condition of all the abdominal viscera. The peritoneal and pleural cavities contain serous fluid stained with the altered blood-pigment.

Nitrites.—Nitrous acid and its salts are poisonous, the effects being the same in kind as those of nitroglycerin and amyl nitrite, but less marked in degree. The nitrites irritate the stomach, dilate the blood-vessels, and convert hemoglobin into methemoglobin. All substances forming methemoglobin cause dilatation of the vessels in all organs. A third symptom accompanying these is a fall in blood-pressure; but it is more correct to say that the diminished pressure is due to the dilatation of the vessels. Binz believes that the other effects are secondary to the reducing action of the poison on the oxyhemoglobin. Collischorm has reported two cases of poisoning with sodium nitrite. The most marked effects were diarrhea, marked cyanosis, and the appearance of an exanthem resembling measles. Bacteria may reduce nitrates to nitrites, but it is questionable whether this reduction ever occurs in the alimentary canal of man.

Cases of poisoning among those engaged in the preparation of **melinite**, an explosive used by the French, have been reported, and are believed to be due to the vapors of nitrous acid. The composition of this substance is, however, not definitely known, except to the manufacturers. Kobert states that carbolic and nitric acids are mixed in its preparation, while others state that it is composed of picric acid, gun-cotton, and gum-Arabic. At any rate, it contains a nitro-body.

Dinitronaphthol, known as Martin's yellow, and dinitrocresol, are employed as artificial coloring agents. Both have a reducing action on the blood; and, according to Kobert, at least one death has been due to dinitronaphthol.

Anilin.—This substance, now so largely employed in the arts, is also a methemoglobin producer. Section shows, after death from anilin, besides the blood-changes, a condition of venous dilatation and possibly blood-extravasations. Multiple capillary thromboses have been reported, but are not always found.

Antifebrin or **acetanilid** has practically the same action as anilin, and its frequent employment as an antipyretic agent in fevers is probably responsible for some deaths attributed to the disease. The same is true of antipyrin, phenacetin, antiseptin, kairin, and other coal-tar derivatives.

ANIMAL POISONS.

The Venoms of Snakes.—Some years ago Mitchell and Reichert made a careful study of the venoms of various serpents, such as cobra, rattlesnake, moccasin, and Indian viper, and succeeded in isolating two proteid constituents: one belonging to the class of globulins, and the other to the peptones. Numerous investigators have practically confirmed this work. However, there are some reasons for believing that the poison classed by Mitchell and Reichert among the peptones is, more properly speaking, an albumin. The poisonous globulin, although present in smaller quantities than the peptone, induces the same remarkable effects locally when injected as are seen after snakebite or after injection of the whole venom. Necrosis of tissue results, the capillaries are corroded, local hemorrhage occurs, and the coagulability of the blood is destroyed. The globulin has not only a local action, but may have a paralyzing effect on the peripheral ends of the splanchnics, on the vasomotor center, and on the heart. Feoktistow found that the poisonous globulin paralyzed the respiration, after which the heart beat feebly for a few moments, but not with force enough to carry the blood into the vessels. He found profuse blood-extravasations in all the organs of the abdomen and thorax. The pericardium was often filled with blood, and hemorrhage into the intestines was sometimes observed. The urine also contained blood.

The venom peptone from the rattlesnake causes an edematous swelling about the point of injection. The subcutaneous tissue becomes infiltrated with serum and rapidly breaks down, forming an extensive slough.

In one bitten by a poisonous snake, the parts above the wound soon become blue and swollen, the swelling rapidly involving the whole of the injured extremity and even extending to the trunk. The swollen parts become dotted with petechiæ. The local effects may gradually disappear and recovery slowly follow. In fatal cases, the heart beats feebly, there is great dyspnea, and convulsions at times occur.

Section shows the serous infiltration already mentioned. The serous membranes generally exhibit numerous hemorrhagic spots. The lungs are hyperemic, frequently edematous. The mucous membrane of the stomach and intestines is often dotted with ecchymoses, and the intestines may contain considerable blood. Focal necrosis occurs. The blood in the larger vessels is dark and fluid. Bacteria speedily find their way from the intestines into the tissue, and putrefactive changes rapidly progress.

The blood of many nonpoisonous snakes, as the common garter-snake, is poisonous when injected intra-abdominally into guinea-pigs in quantities of 1.5 c.c. The symptoms and postmortem appearances thus induced resemble those caused by the bite of a venomous serpent.

Immunity to the venom of snakes is rapidly acquired by many animals, as was first shown by Sewall; and animals thus immunized furnish, as Fraser and Calmette have shown, an antitoxin which is successfully employed in the treatment of snakebite.

The uncooked blood of the common river-eel, the Conger eel, and the murena is quite poisonous. Mosso calls the active principle ichthyotoximum. When applied to the tongue, it burns like phosphorus; subcutaneously it causes marked local reaction.

Fish Poisoning.—Some fish, such as *Trachinus draco*, are supplied with

poisonous glands connected with barbs. Sometimes bathers and fishermen are wounded with these barbs, and fatal results may follow. Locally there is edema, which may be followed by gangrene.

Kakke, a disease prevalent in Japan and other countries along the eastern coast of Asia, is believed by Miura to be due to the eating of fish belonging to the Scombridæ.

According to Remy, there are twelve species of tetrodon the ovaries of which are poisonous, and Tahara reports that he has isolated two poisons from the roe: one, a crystalline body, he names tetrodonin; the other, a white waxy substance, he calls tetrodonic acid.

Fish poisoning so frequently observed in the West Indies is believed to be due to the fact that the fish feed upon decomposing medusæ and corals. The symptoms are those of gastro-intestinal irritation.

Fish may be infected with pathogenic bacteria; and these or their chemical products, when taken by man in his food, may prove deleterious. Recent studies indicate that the Russian epidemics of fish poisoning originate in this way.

In our own country, poisoning with canned fish is the most frequent form of ichthyotoxism. This is due to the growth of toxicogenic bacteria in this article of food.

Poisonous Toads.—All toads have poisonous glands, which are seen in the form of warty excrescences on the surface. One of the active agents in the secretion of these glands is phrynin, which, when applied to the mucous membranes of man and other mammals, causes a severe local irritation. Applied to the eye, it causes great pain followed by conjunctivitis and keratitis. Taken internally it acts as an irritant, and when injected intravenously it has a digitalin-like action. Kobert ascertained that toads into which a solution of barium chlorid is injected empty all their poisonous glands, covering the body with a cream-like substance. It is stated that the Indians of New Granada employ the secretion of a pelobate as an arrow-poison, and that deer wounded with the arrows die within four minutes, and jaguars within eight minutes.

Poisonous Salamanders.—The active agent of the poisonous secretion of this animal is an alkaloidal body known as salamandrin. It acts as a local irritant and may induce convulsions similar to those of strychnin. Two milligrams injected intravenously suffice to kill a dog. A hypodermic injection of muscarin causes the salamander to secrete an abundance of this poison. The secretion of the water salamander is less poisonous than that of the fire salamander; but it also may cause severe local inflammation, especially when applied to the eye.

Poisonous Scorpions.—The posterior segment of this animal is supplied with two poison-glands connected with the barbed tail. The secretion is a clear, acid fluid. It induces local inflammation and resembles the poisons of the toad and salamander.

Poisonous Spiders.—All true spiders are supplied with poisonous glands; and besides these organs, some secrete from the entire surface of the body a poisonous substance. The secretion of the glands is a clear, oily, acid fluid, which varies in intensity of effect in different species. Among the best known of the more poisonous spiders may be mentioned the tarantula, the malmignette, and the katipo. The secretion of the malmignette is believed to be the most active of all animal poisons. In the southeastern part of

Russia, camels, sheep, and horses, as well as men, sometimes die from the bite of this spider. The local reaction is slight or wholly unobservable. Death generally follows a long-continued and painful paralysis of the extremities. The local effects of the bite of the tarantula consist of swelling, infiltration, and possibly necrosis. It is believed that the active agent in the poisonous secretions of spiders is a proteid, but we have no positive knowledge on this point.

Spanish Fly.—Cantharidin, the active principle of this beetle, is stored in largest quantity in the sexual organs. The dried beetle contains about $\frac{1}{2}$ per cent. of the poison. There is also present a volatile oil, of characteristic odor; and this, as well as the cantharidin, acts as a local irritant. Cantharides is known to be one of the most active vesicants. The serum that collects in a Spanish-fly blister is characterized by the small number of leukocytes present. It is supposed that cantharidin has a paralyzing effect on the leukocytes. Taken internally, this substance acts as an irritant on the digestive organs and kidney. A glomerulonephritis, with blood and casts in the urine, may be due to internal administration or to the application of a large blister. There may also be desquamation of the epithelium of the bladder.

Bees and Ants.—The poisonous secretions of bees and ants contain formic acid and undecan. The sting of a bee is usually followed only by slight pain and swelling. However, if the sting be left in the skin, supuration may result; this is probably due to infection. When the sting pierces a blood-vessel, death may result from the formation of thrombi. A sting on the tongue or in the pharynx may cause an edema of sufficient extent to lead to death from suffocation. When many bees sting a man, there may be delirium, coma, and death, without thrombi.

BACTERIAL POISONS.

This is not the place to discuss the pathology of the toxins of the specific pathogenic bacteria; such a discussion would properly come under a description of the specific diseases. We will proceed to a very brief statement of the pathologic conditions induced by certain nonspecific toxicogenic bacteria that sometimes occur in articles of food.

Meat Poisoning; Botulismus.—Postmortem examination after sausage poisoning, as a rule, shows no characteristic lesion. Some have stated that putrefaction sets in very tardily; but no reliance can be placed upon this, since Müller found that, out of forty-eight recorded autopsies, it was especially stated in eleven that putrefaction rapidly developed. In some instances hyperemia of the stomach and intestinal canal has been observed, but this is by no means constant. The liver and brain have been reported as congested; but this condition might result from failure of the heart, and would be by no means characteristic of sausage poisoning. Von Faber held autopsies upon four persons killed by eating poisonous sausage. The skin was rough, the abdomen was retracted, the large vessels in the upper part of the stomach were filled with dark blood. The contents of the stomach consisted of a reddish-brown semifluid substance giving off a repugnant acid odor. In one of these cases the omentum was found to be greatly congested. The large intestine was very pale, and the right ventricle of the heart was filled with dark fluid blood.

In cases recently studied at the University of Michigan, a severe follicular enteritis of the small intestine was found. The solitary glands and Peyer's patches were greatly swollen, showing on microscopic examination edema, small-cell infiltration, and necrosis of the central portion. Numerous small hemorrhages, and shallow ulcerated patches of irregular size and distribution, occurred throughout the mucosa. The entire colon showed a very marked diphtheritic colitis, with large irregular ulcers extending to the muscular coat, which in some places showed a marked small-cell infiltration and edema. The blood-vessels throughout were greatly congested and showed a leukocytosis. The kidney presented the picture of an acute parenchymatous nephritis added to that of a chronic nephritis. All of the cells of the convoluted tubules showed extensive cloudy swelling and fatty degeneration, and areas of hemorrhagic and leukocytic infiltration occurred throughout the cortex.

In animals killed by being fed upon poisonous sausage, Ballard found that most of the urinary tubules contained casts, while many of the Malpighian bodies with their surrounding tissue were in a state of disintegration—without, however, any inflammatory cells being present, thus indicating that the disintegration was the direct result of some destructive agency circulating in the vessel. In some cases of poisoning from tinned salmon, Klein found necrosis of the superficial layers of the mucous membrane of the stomach, fatty changes of the liver resembling those of acute poisoning with phosphorus, and also inflammation of the kidneys. Mice fed upon this salmon died, exhibiting lesions similar to those found in man. In some cases of poisoning from veal pie, the same authority found that animals fed upon this food showed no ill effects until the feeding had been continued for three days, after which some of them died; postmortem examination gave evidence of intestinal inflammation and congestion of the kidneys. In still other animals killed by cultures obtained from poisonous meat, Klein found that the liver and kidneys were congested and dark, while the lungs were dark red and almost hepatized. The small intestines were relaxed and filled with mucus.

Gärtner observed desquamation of the epidermis in persons poisoned with meat; even boiled cultures of the germs obtained from this meat were found to be highly poisonous.

Lubarsch reports an interesting case in which the anatomic examination showed pleuritis and pneumonia of the left lower lobe, bilateral bronchitis, atelectasis of the right lung, granular changes in the kidneys, infiltration and engorgement of the liver, slight enlargement of the spleen, uric acid infarction of the kidneys, and icterus. In all animals poisoned with the germ obtained from this case, section showed marked congestion of the intestines, swelling of the follicles, and in some instances slight hemorrhages in the mucous membrane. After intraperitoneal inoculation, serofibrinous or hemorrhagic peritonitis developed. After subcutaneous inoculation in rabbits, there was a serofibrinous pleuritis with compression of the lungs, and in one instance a circumscribed pneumonia. Animals inoculated by Basenau with the poisonous germ obtained from meat showed the following condition: The tissue about the place of inoculation broke down, forming a yellowish-white structureless mass. The surface of the liver was covered with pin-head grayish-white foci of inflammation, giving to the organ a marbled appearance. The spleen showed a similar condition, and both organs were somewhat enlarged.

Animals inoculated with a poisonous germ obtained by Perkins and the writer from some pressed chicken, that had seriously affected a large number of people, showed evidences of abdominal pain within from one to two hours, and several of them were found dead after twelve hours. The abdominal cavity was filled with a clear fluid, the blood-vessels were much congested, and the peritoneum reddened. In some instances a bloody fluid was found in the pleural cavity.

Van Ermengen has isolated a poisonous bacillus from meat, and his observations have been repeatedly confirmed by others.

Poisonous Milk and Cheese.—Up to present writing, the poisons formed in cheese are apparently due to three classes of germs, which vary markedly in their virulence. One class of these germs produces a highly poisonous basic substance, to which the name tyrotoxicon has been given. After experimental poisoning with tyrotoxicon, the mucous membrane of the stomach and intestines is found to be very pale. The most characteristic postmortem condition consists of tightly contracted areas in the intestines. Another class of cheese-germs produces a poison which has not as yet been isolated, and which has a muscarin-like action, but induces no characteristic postmortem lesions. A third class of harmful germs found in cheese belongs to the colon group. The symptoms and postmortem appearances induced by this group vary greatly, as the virulence of the germs themselves is subject to great variation. An animal inoculated with a poisonous germ obtained from this class of cheese may show no anatomic lesions, while, on the other hand, there may be marked hemorrhages in the omentum, the mesentery, and the walls of the intestines.

THE GENERAL PATHOLOGY OF FEVER.

BODILY TEMPERATURE.

THERE is no more wonderful phenomenon in the animal economy, perhaps, than the constancy of the bodily temperature. Notwithstanding great variations constantly taking place in the production of heat and in the loss of heat, the temperature of the body does not vary more than 1° C. in man. In the lower homoiothermal animals the variation is distinctly greater than in man, but even in them the temperature is remarkably uniform. Before considering the abnormality of these functions in fever, let us consider briefly what conditions influence the heat-processes normally and how the normal bodily temperature is maintained.

NORMAL VARIATIONS OF BODILY TEMPERATURE.

The temperature of man varies according to the part of the body at which it is noted. According to Pembrey, the mean daily temperature of the axilla is 36.9° C. (98.45° F.); that of the mouth, 36.87° C. (98.36° F.); that of the rectum, 37.2° C. (98.96° F.). Of course, there is some variation of a fraction of a degree from these figures in either direction in different individuals.

Time of Day.—The temperature of man is subject to slight diurnal variation, rising during the afternoon and early evening until the maximum is reached at from 5 P. M. to 9 P. M. There is a steady gradual fall from this time till early morning, the minimum usually occurring between 2 A. M. and 4 A. M. This variation is usually less than 1° C.; it is generally attributed to muscular activity and taking food during the day, although the writer found the same diurnal rhythm to exist in rabbits deprived of food and exercise.

Muscular exercise may, if it be violent and continued for an hour or longer, cause a transitory rise of temperature of one degree or so for a very short time, but this rapidly disappears after the exercise ceases. The production of heat is increased enormously by muscular work, but it is usually compensated for by increased loss of heat during and soon after the exercise.

Food.—There may be a slight rise of temperature after a hearty meal; here again increase of the heat produced is rapidly balanced by increase in the heat-loss. Abstinence from food causes the bodily temperature to fall slightly.

External temperature causes slight variation in the bodily temperature. The temperature of man in the tropics is not over 0.5° C. above that observed in temperate climates, while the temperature of men in Arctic regions shows no greater variation in the other direction; further, the temperature of animals in Arctic regions is the same as that of animals of the

same classes living in temperate climates. The external temperature, then, may vary from $+50^{\circ}$ C. to -50° C., while the bodily temperature will not change more than 1° C.

As to the extremes of external heat or cold that can be borne with impunity, much depends upon the degree of moisture present in the air. James found that 80° C. caused little inconvenience as long as the air was dry, while a vapor bath at 44.5° C. could only be tolerated a short time. A moist air at 45° C. will soon cause a rise of bodily temperature.

Water is a much better conductor of heat than air, and, further, prevents evaporation. A cold bath can be resisted by a normal man for a considerable time without much reduction of temperature, although the loss and production of heat must be enormously increased. Thus, remaining in a bath at 25° C. for three hours caused a fall of temperature of but 0.6° C.; a bath at 15° C. for the same length of time caused a fall of only 1° C.

On the other hand, a warm bath will raise the temperature of the body after a few minutes, although it may not be nearly so much above the temperature of the individual as the cold baths just mentioned are below it. Remaining in a bath at 45° C. for ten to twelve minutes will cause a rise of bodily temperature of 2.5° C., which rapidly disappears after leaving the bath.

Age seems to have very little influence on the degree of temperature. The surface-temperature of the aged may be lowered from imperfect circulatory conditions, but the rectal temperature is unchanged. The temperature of infants may be a trifle higher than that of adults, but this is insignificant. The *instability* of the temperature of children, however, is very pronounced and characteristic. Slight causes which would not affect the temperature in adults will cause a tremendous elevation of temperature in children.

CONDITIONS INFLUENCING HEAT-PRODUCTION OR THERMOGENESIS.

Muscular Exercise.—It is estimated that the production of heat is from one to three times greater during muscular exercise than during rest.

Food.—The production of heat is from 30 to 40 per cent. greater when food is taken than when it is withheld; there is considerable increase after each meal. The character of the food also influences the amount of heat produced, fats being more than twice as valuable in this respect as either proteids or carbohydrates.

Conditions Affecting Heat-Dissipation Primarily.—**Size.**—Generally, among animals of approximately the same size, the production of heat depends upon the body-weight. However, when there is a great difference in size, the smaller ones produce relatively much more heat than the large ones. This is because the external surface is much greater as compared with the bulk, and the loss of heat is in proportion to the extent of surface. The production must balance the loss, to maintain the bodily temperature.

External Temperature.—A low external temperature increases the production of heat, because the loss of heat from the body is greater notwithstanding the efforts of Nature to limit the latter. On the other hand, a high external temperature may lessen the heat-production to a certain extent; but this diminution cannot be as great as the increase in a cool environment.

The muscles constitute from 42 to 45 per cent. of the body-weight; and as the greater part of the chemical changes of the body occurs in them, they form the chief seat of the production of heat in the body. As the heat produced in other tissues is

tolerably constant, it is highly probable that variations in thermogenesis are caused chiefly by variations in the heat produced by muscles. According to Stewart, removal of the nervous control of voluntary muscles by poisoning with curare reduces their metabolism to one-fifth of the normal and reduces the total heat-production of the body 35 per cent. He divides the remaining 65 per cent. as follows: Heart, 15; skeletal muscle, 10; all other tissues, 40. Of course, when muscles are contracting, heat is necessarily produced in great quantities, as four-fifths of the energy expended reappears as heat. But even when there is no mechanic work performed at all, the muscles produce nearly as much heat as all the other tissues of the body put together. All the chemical potential energy may be converted into heat, or a part of it may appear as work.

The heat-production and heat-dissipation can only be measured for short periods of time with any accuracy by either air or water calorimeters. Unfortunately calorimeters large enough to admit men are not very accurate, although small ones for animals may be fairly constant. However, the measurement of heat-loss and heat-production is not as simple or easy a matter as it might appear. Measurements of heat lost to water by placing a man in a bath are worthless, as at most only the heat from the skin could be recovered; while the water, being so much more conductive of heat than air, places the individual under abnormal conditions.

The respiratory quotient ($\frac{\text{CO}_2}{\text{O}_2}$) may be taken as an index of combustion in the tissues, and thus indirectly of heat-production, if the diet be unaltered. This is not so valuable when used for short periods of time, as oxygen may be stored in the tissues for some time, and altered conditions of the blood may influence the CO_2 given off.

Methods of measuring the heat produced, by calculations from the heat values of the foodstuffs absorbed and excretions given off, are of little use in the study of fever. Both the production and the loss of heat are fluctuating, and at best no idea of the relation between the two could be gained. In most cases of fever, disintegration of the permanent tissues is going on to a great extent.

CONDITIONS AFFECTING HEAT-LOSS OR THERMOLYSIS.

From 75 to 80 per cent. of the heat lost from the body is given off by the skin, chiefly by radiation and conduction, and to a much less extent, under ordinary conditions, by evaporation. The lungs give off from 15 to 18 per cent. of the total heat-loss, chiefly by evaporation and to a much less extent by warming the air.

Heat-dissipation or thermolysis will, therefore, depend upon the following conditions: The covering of the body, the external temperature, the condition of the blood-vessels on the surface and the rapidity of the circulation, the activity of the sweat-glands, the deposit of subcutaneous fat, the relative humidity of the air, and the volume of air moved in and out of the lungs. Of course, anything primarily affecting heat-production—*e. g.*, food, exercise, etc.—will, in the normal body, affect heat-loss secondarily. Small animals lose much more heat per kilo. of body-weight than large ones, their surface being proportionately much greater.

There is no daily variation in the heat-production and heat-dissipation corresponding to the diurnal rhythm of bodily temperature.

THE MAINTENANCE OF A CONSTANT TEMPERATURE.

However great the variations, both of heat-production and of heat-loss, from hour to hour, caused by the many conditions of daily life, the bodily temperature is but little affected by any of them. The temperature does not depend upon either the one or the other alone, but upon the *relation between the two*. The balance can only be maintained by some regulating mechanism which can control both processes, so that when one is affected primarily the other may be adapted accordingly. Thus, when the produc-

tion of heat is increased from exercise, the dissipation is changed correspondingly by accelerated respiration and circulation, dilated peripheral vessels, and active sweat-glands. On the other hand, when heat-loss is primarily increased, as by exposure to low external temperature, the superficial vessels constrict to keep the blood from the surface. Nature makes every effort to reduce the thermolysis to a minimum; but if it be still increased, the production of heat increases to keep pace with it.

Ordinarily the regulation of bodily temperature is effected chiefly through changes in thermolysis, and the range of variation in loss of heat from the body is a wide one. The means of increasing or decreasing heat-dissipation are numerous, provided surrounding conditions are favorable for such changes. When, however, the temperature of the atmosphere is near that of the body and contains a high percentage of moisture, the limit of regulation is soon reached, because the dissipation cannot be increased as usual.

Although the production of heat may be increased in a *low* external temperature, it cannot be decreased in a *high* external temperature as much as is often supposed.

Altogether, extremes of cold can be borne with less discomfort than extremes of heat; it is a remarkable fact that the bodily temperature may be reduced as much as 12° C. (21.6° F.) and recovery occur (Nicolaysen), while an increase of half that amount is extremely dangerous and usually fatal.

Reasons for Believing the Nervous System is the Controlling Factor.—From the great and constant variations, both of thermogenesis and of thermolysis, it is hard to conceive how the regulation of bodily temperature or thermotaxis can be brought about in any other way than through the influence of the nervous system. Although the various means of thermolysis have long been recognized as governed by nerve-centers, the control of heat-production or thermogenesis, and of heat-regulation or thermotaxis, by the nervous system, has been much more difficult to prove and has only been established in recent times. While there can be no doubt as to the main facts, the exact functions of some so-called “heat-centers” have not been made clear.

Bernard's observation on the rise of temperature in the rabbit's ear after section of the cervical sympathetic was the starting-point of our knowledge of the influence of the nervous system on the heat-processes. His view that the rise of temperature was independent of the vascular change and due to the removal of an inhibitory influence over the heat-production in the tissues has not been confirmed by others. Similarly the alterations of temperature resulting from stimulating sensory nerves or the spinal cord, as recorded by Heidenhain, Riegel, and Tangl, were doubtless brought about by changes in the circulation.

It is unnecessary to assume that there must be specific thermogenetic nerve-fibers for such a nervous control. It is sufficient to prove that the chemical changes taking place in the tissues are regulated by the nervous system, and that such changes can be varied independently of the ordinary performance of work by the various tissues. The most valuable experiments in this direction are those showing great alterations in metabolism from removal of the nerve-control of muscles by poisoning with curare. Curare produces paralysis of the motor nerve-plates, vasodilatation, and causes the bodily temperature to fall, if the temperature of the air is lower—or to rise, if the temperature of the environment is higher—than that of the

body. Even if the normal bodily temperature be artificially maintained, the gaseous interchange is greatly altered—the intake of oxygen falling about 35.2 per cent. and the output of CO_2 falling 37.4 per cent. When the temperature of the animal is raised artificially, the respiratory exchange is increased; when lowered, it falls. These changes are not due to a deficient supply of oxygen, as it was abundantly furnished by artificial respiration. They are not due to any direct action on the sarcois substance, as muscles artificially perfused with blood containing curare show the same oxidation as when the blood does not contain the poison. The only explanation is the separation of the muscles from the nerve-centers governing them; and as the muscles produce most of the heat of the body, thermogenesis is very materially affected. The mere diminution of heat-production and of these chemical changes is no more significant than is the fact that heat-regulation or thermotaxis is lost, so that a homoiothermal or so-called warm-blooded animal becomes a poikilothermal or so-called cold-blooded animal under the influence of curare. The animal can no longer adapt its heat-processes to the environment, and the bodily temperature varies with external changes. This is not due merely to the vasodilatation, but chiefly to the paralysis of the voluntary muscles.

Section of the spinal cord high up in the cervical region removes the power of thermotaxis. The bodily temperature rises with high external temperature or excessive covering of the body, and falls with low external temperature. The production of heat is lessened by the muscular paralysis, while the loss is increased by the vasodilatation. Thermolysis may also be interfered with by disturbances of respiration and sweating.

Generally the bodily temperature falls after injury of the spinal cord. A few cases of hyperpyrexia after injuries of the cord have been recorded; it is difficult to explain these.

Efforts to localize "heat-centers" in the brain have led to conflicting and confusing conclusions. The claims of different investigators are so at variance that no definite function can be attributed to these various centers. The most we can say is that injury of certain parts of the brain produces a rise of temperature with consequent changes of metabolism, the elevation of temperature lasting a variable time.

The parts, injury to which has these effects, are as follows: 1. Cortex: (a) The neighborhood of the cruciate fissure and just back of it (dogs and cats); (b) the junction of the supra-Sylvian with the post-Sylvian fissure (cats). 2. Basal ganglia: (a) Pons; (b) corpus striatum (dogs, cats, and rabbits); (c) optic thalamus (rabbits only).

Most of these experiments have been performed upon rabbits. The temperature of these animals is unstable and easily influenced by slight disturbances. Injury to some of the areas claimed to be heat-centers in rabbits does not cause rise of temperature when occurring in corresponding areas in dogs. On the other hand, the operative procedure in some of the experiments upon dogs is enough to produce such a condition of shock as to vitiate any results.

Again, different conclusions have been reached concerning the same area. Thus, the first experiments showed that section between the pons and medulla caused rise of temperature and increased heat-production and heat-dissipation. The conclusion was that there was an inhibitory center in the pons or above it which normally controlled a hypothetic augmentor center in the medulla (Tschesichin, Wood). Subsequent observers found that such sections produce a fall of temperature as often as they cause a rise, and further that puncture with a probe or electric stimulation of the pons will cause quite as great a rise; and they reach the conclusion that the center in the pons is an augmentor center (Bruck-Günther, Schreiber).

Another observer (Ott) produced rise of temperature by puncturing the pons, but claimed that he had injured fibers from higher centers and not nerve-cells. The same observer, however, has attributed similar results after injuries to the basal ganglia to injuries of nerve-cells.

Areas in the cortex are claimed to be thermo-inhibitory because a rise of temperature ensues when they are injured, while other areas in the basal ganglia are assumed to be augmentor, although similar injuries with a probe cause a rise of temperature.

One observer considers the cortical centers to be thermotactic, while another considers them to be thermogenetic, because the fever is established with an increase of heat-production. Pyogenic poisons are generally supposed to act upon thermotaxis.

Some experiments by Ott indicate that injury of the corpus striatum interferes with the rapid respiration (polypnea) produced by exposure of furred animals to hot air. He calls this a thermopolypneic center; he also claims vasomotor changes from injury of the optic thalamus. If these are correct, these parts are concerned in thermolysis. In another communication Ott claims these centers are thermo-inhibitory (*i. e.*, thermogenetic); at another time he considered the centers in the basal ganglia as thermotactic. Calorimetric experiments do not indicate that thermolysis or heat-dissipation is primarily disturbed by puncture of these centers. It is not clear why destruction should act in the same way as electric irritation by the Faradic current, as Aronsohn and Sachs obtained the same result by either method; or why one center in the cortex should be considered thermotactic, while another at the base, which when destroyed in the same way causes fever to be brought about in the same manner, should be considered thermogenetic. Some of the experiments are not conclusive, while certain deductions drawn from them are not justified.

FEVER.

Definition; Stages.—The term fever is sometimes used loosely to signify a mere rise of temperature above normal. There are, however, conditions of elevated temperature which are not febrile—*e. g.*, the transitory rise of temperature after a hot bath or from violent exercise, in either of which the condition is within physiologic limits. So, too, the mere rise of temperature in children caused by crying or teething, or the sharp rise of temperature sometimes seen in hysteria and occasionally from passing a catheter without infection (“urethral fever”), probably may be regarded as due to a temporary disturbance of the normal regulation of the heat-phenomena of the body, without the usual conditions occurring in fever.

The pathologic state, *fever*, is indicated by a group of symptoms as follows: (*a*) Rise of temperature, (*b*) altered metabolism, (*c*) increased activity of circulation and respiration, (*d*) functional changes, (*e*) structural alterations in various tissues of the body. Of these conditions the first two are the most important, and the functional and anatomic changes may result from them. Generally the poisons causing the rise of temperature also produce all the other conditions. Sometimes these conditions, which are often regarded as secondary, are out of proportion to the elevation of temperature, as is quite often the case in diphtheria.

On the other hand, the mere pyrexia or elevation of temperature alone may be primary, and all the other conditions secondary, as is clearly the case in thermic fever and probably in that produced by injury of nerve-centers.

While the rise of temperature (pyrexia) is the most prominent and most constant condition, it is not an absolutely essential symptom of fever. Sometimes in septicemia, and very rarely in typhoid fever, the other conditions of fever may be present without elevation of temperature. Indeed, in uremia, the same poisons which at times cause marked pyrexia may in other cases cause a fall of temperature. Considerable confusion has arisen from apply-

ing different meanings to the word "fever." Perhaps it would be better to use "fever" to include the entire group of phenomena, and "pyrexia" for the most conspicuous one—the rise of temperature.

We generally estimate the severity of the fever by the degree of pyrexia, although, as has just been said, this is not always an index. Thus, when the temperature is not over 37.7° C. (100° F.), it is spoken of as "slight fever"; between 37.7° and 39.4° C. (100° – 103° F.), it is considered as "moderate fever"; between 39.4° and 40.5° C. (103° – 105° F.), it is "high fever"; while over 40.5° C. (105° F.), it is regarded as "hyperpyrexia."

The course of most fevers can be divided into three stages, as follows: 1. The *initial* or "*cold*" stage, when the temperature is rising. 2. The *fastigium* or "*hot stage*," when the temperature is at a fairly constant level above the normal. 3. The *terminal stage*, the *period of decline or defervescence*, when the temperature is falling.

The **initial stage** usually starts with chilliness, and often with a distinct chill if the onset be sudden. The patient feels cold and the surface-temperature may be subnormal, although the internal temperature has already risen considerably above the normal. The elevation of temperature precedes the chill, although it is still rising during the cold stage. The rigor or shivering may increase the heat-production from muscular contraction. The skin is generally pale, but is sometimes cyanotic. Although the heat-loss from the surface is diminished in this condition, it is not the primary cause of the rise of temperature. Studies of malarial fever with the plethysmograph show that the elevation of temperature antedates the vasoconstriction of the surface-vessels.

The **second stage** or **fastigium** varies from a few hours to as many weeks in duration. Usually when the subjective sense of chilliness passes off, the temperature has attained its height. The cutaneous vessels dilate and the skin is flushed. It feels hot and dry to the touch, but the actual amount of sweat from the surface may be increased even in this condition. The internal temperature is tolerably constant, but may fluctuate considerably. The diurnal variation, with the maximum in the evening and the minimum in the morning, is usually present, but is not as regular as that seen normally. The surface-temperature is subject to wide variations during this stage.

The **terminal stage** may occupy several days, the temperature gradually falling a little lower on each successive day (termination by "lysis"). It may occupy but a few hours, when the fever is said to end by "crisis." In this latter condition there is profuse perspiration, or sometimes diuresis and acceleration of the respiration. The great increase in the heat-loss indicates an effort to restore the bodily temperature to normal.

DISTURBANCE OF THE HEAT-PROCESSES IN FEVER.

As the elevated temperature is the most conspicuous and most constant condition of fever, the question is naturally suggested: How is this rise of temperature produced?

Theoretically the condition could be effected in a number of ways or combinations of disturbances of thermogenesis and of thermolysis.

Clinical observation alone would lead us to suppose that there is tremendous diminution of heat-loss during the initial stage, and a corresponding

increase during the terminal stage. This would indicate that fever is due to heat-retention; but this theory (Traube's theory) is no longer held, for it has been found that usually the increase of production is greater than the decrease of heat-loss during the initial stage. Moreover, the rise of temperature precedes the cold stage. During the fastigium or hot stage, the hot and dry skin alone would lead one to suppose that loss of heat by evaporation is greatly decreased, although the loss by radiation and conduction is increased. We still need more extensive and accurate measurements of the former means of heat-loss, but the observations recorded indicate that the loss of water from the skin may be increased, although the skin feels dry.

Clinical observations as to the condition of the skin do not give accurate information as to the total heat-loss, the heat-production, or the relation between the two. These can only be determined by calorimetric observations. Unfortunately an apparatus large enough to contain a man has not been constructed so as to give constant and accurate results. Efforts to

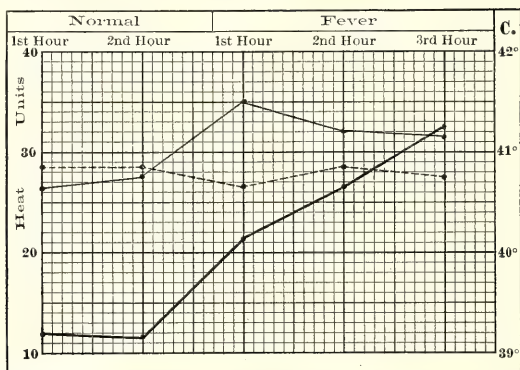


FIG. 136.—Composite curve showing how pyrexia is produced. Heat-units on the left; degrees of temperature (Centigrade) on the right. Continuous line represents heat-production; dotted line represents heat-dissipation. Heavy line below represents the temperature.

measure the heat-loss by placing a febrile patient in a bath, as was done by Liebermeister, or by placing one limb in a calorimeter, a method followed by Leyden and by Rosenthal, are open to much criticism.

The most reliable information as to the heat-processes in fever is derived from calorimetric observations on animals made febrile experimentally. But even the smaller instruments are not as accurate as they might be. A careful examination of the changes of temperature, compared with the changes in the production and loss of heat, will show many discordant results; but we can accept the gross changes, as they are quite constant.

Experimental evidence indicates that there is an increase in heat-production in pyrexia, over the heat produced by the normal animal in the fasting state; but less is produced than in a condition of health on a full diet. The total average increase is not over 25 per cent. of the normal, under similar conditions of diet. The increase, however, is not as great as the hot, dry skin during the hot stage of fever would lead one to infer.

Indeed, the increase is greater in the early stage during the *establishment* of the fever than during its *continuance*, as can be seen by examining the curve in Fig. 136. This is a composite curve made from twenty calorimetric experiments on dogs, the fever having been produced after the second hour by the intravenous injection of putrid blood (5 drops) every hour.

Although the heat-loss is less during the establishment of fever than during its height, it is usually greater than the normal. *In experimental fever at least, the pyrexia appears chiefly to be due to increased production rather than to diminished loss of heat.* Exceptionally it happens that fever is established by a great diminution of thermolysis without any increase of thermogenesis.¹ Possibly, as W. Hale White pointed out in his Croonian Lectures,² we are too prone to generalize and apply these results to all fevers in man. White contends that pyrexia in man is established in some cases by increased thermogenesis, in others by diminished thermolysis. While this may be true, his method of determining heat-loss and heat-production from the internal temperature, the surface-temperature, and evaporation of sweat, is not beyond criticism. Of course, if both conditions are present, they conjoin to produce a still greater rise of temperature.

During the stage of defervescence, the production of heat falls and its dissipation increases, the latter being out of proportion to the former when the fall is rapid. This change can be seen by the curve in Fig. 137. This is a composite curve representing five experiments of two days each. The curve on the left shows how fever was established the first day; that on the right the normal the first hour, the production of fever by giving the same amount of putrid blood as the day before (5 drops) every hour after the first hour, and the reduction of temperature beginning the third hour, one hour after its administration by the stomach. The average dose of antipyrin was 0.93 gm. per kilo. of body-weight.

In fever, as in health, there is absolutely no relation between the amount of heat produced and the bodily temperature. Although the heat-production is increased on the average, it is no greater than in health on a full diet and probably not as great as in many conditions of health, *e. g.*, muscular exercise, exposure to cold, consumption of large amounts of food. It is therefore evident that *fever does not result from the mere increase of heat-production alone, but from a disturbance of heat-regulation or thermotaxis.* The athlete, in playing a game of football or rowing in a boat-race, probably produces more heat than is produced in the establishment of the most severe fever; but the temperature does not rise, because thermolysis keeps pace with increased thermogenesis. It is this *relation between the two* that is disturbed in fever, and *not the absolute quantity of heat produced.*

This view is rendered the more probable from the way in which most antipyretics act upon *both* the production and the dissipation of heat, to restore the normal temperature (see Fig. 137). Antipyretics do not affect the temperature of the normal animal materially, and neither do they affect heat-production or heat-dissipation, as can be seen in Fig. 138.

Agents which produce pyrexia probably do so by acting upon nerve-centers which regulate the heat-processes of the body (thermotactic centers).

The theory of Liebermeister, that in fever there is still thermotaxis, but

¹ Ott, *Journ. Nerv. and Mental Diseases*, 1889; Wood, Reichert, and Hare, *Therapeut. Gaz.*, 1896.

² *Brit. Med. Journ.*, 1897, vol. ii., p. 1653.

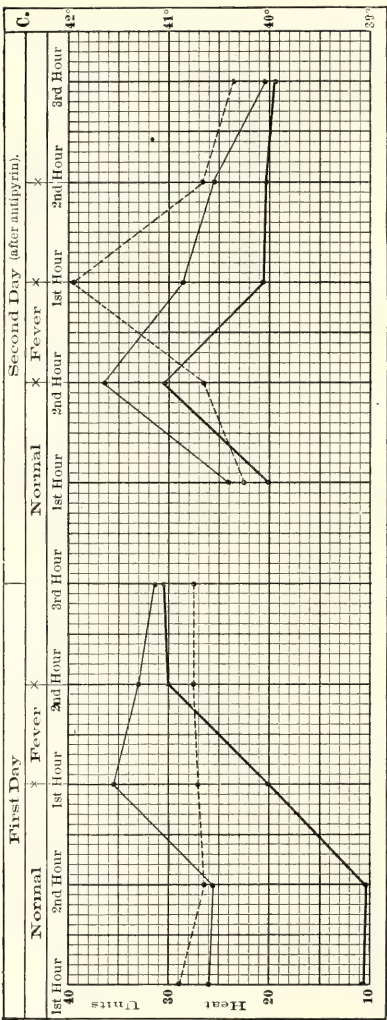


Fig. 137.—Composite curve from five experiments. Continuous line = heat-production; dotted line = heat-dissipation; heavy line = temperature. Fever produced after second hour on first day; after first hour on second day. 0.93 gm. antipyrin by the stomach at second hour, second day. * marks the injection of 5 drops of putrid blood.

simply set for a higher level, just as we would set the thermostat of an incubator in the laboratory for a temperature several degrees above that ordinarily used, is no longer tenable. According to this theory, to quote

MacAllister, man's thermal mechanism in fever would simply correspond to that of a bird under normal conditions.

We have already seen that normal thermotaxis is remarkable for its *stability*. The temperature in fever is characterized by its *instability*. The surface-temperature is constantly changing within wide limits and independently of the rectal temperature. The internal temperature is not subject to as great fluctuations as that of the surface, but varies vastly more than in the normal state and is very unstable, being easily changed to a great extent by agents which scarcely affect the normal temperature. Cold baths and antipyretic drugs cause a tremendous fall of temperature in fever, but not in the normal animal.

Baths seem to do far more good in restoring heat-regulation in fever than in the mere physical abstraction of heat. They probably act on the nerve-centers reflexly through the skin to re-establish thermotaxis.

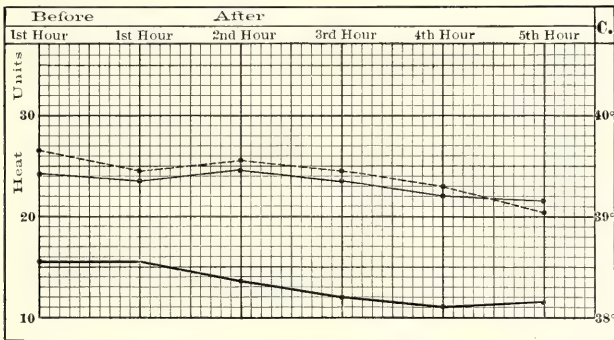


FIG. 138.—Composite curve of eight experiments, showing effect of antipyrin on normal animals. Continuous line = heat-production; dotted line = heat-dissipation; heavy line = temperature. Average dose hypodermatically = 0.19 gm. per kilo.

Welch¹ has also shown in his Cartwright Lectures that rabbits made febrile by puncture of the corpus striatum are unable to withstand exposure to an atmosphere of either high or low temperature without showing far greater variations of the bodily temperature than a normal animal shows.

All these facts point to the conclusion that in fever there is a lack of thermotaxis or heat-regulation.

CAUSES OF DISTURBANCES OF THERMOTAXIS IN FEVER.

Injury of Nerve-centers.—We have already considered the parts of the brain, injury to which, in the lower animals, produces fever. Clinical reports of lesions of these parts in man indicate that they control the heat-processes, and, when disturbed, fever is caused—just how, we cannot say. The inability of animals to adapt themselves to different external temperatures, after injury of some of these centers, would indicate that they are thermotactic. On the other hand, the fever lasts but a short time after such injury, and it is remarkable how constantly the pyrexia is established by

¹ *Med. News*, April and May, 1888.

increased thermogenesis alone. Perhaps the highest temperatures in man are those caused by lesions of the pons Varolii.

Exposure to high external temperature, particularly if the air contains a high percentage of moisture, in a short time causes the bodily temperature to rise to a height seldom seen in specific infections. The condition seems to result from a loss of control of the heat-processes by the nervous centers in consequence of overstimulation or overactivity of the mechanism in the effort to regulate the temperature under such unfavorable circumstances.

Although the rise of temperature is apparently the primary disturbance in this condition, increased oxidation and the usual alterations of metabolism, functions, and structure follow if the pyrexia continues any length of time.

The toxicity of the blood in thermic fever probably results from the disturbance of metabolism brought about by the pyrexia.

Poisons.—Some drugs act as pyretics, as atropin, strychnin, cocain, and caffein; also numerous substances, such as β -tetrahydronaphthylamin, commercial peptone, papoid, pepsin, etc. The pyrogenic agent of the latter seems to be a peptone.

By all means the most frequent causes of fever in man are the products of bacteria (toxins), which probably act in some way upon nerve-centers to produce pyrexia.

By some it is supposed that these poisons act directly upon the tissues to produce fever (the so-called hemic theory of fever). Such action could only produce pyrexia by increasing the heat-production, and we have already seen that fever is due not merely to an increase of production, but to a disturbed relation between thermogenesis and thermolysis.

Pyretic drugs, as cocain and caffein, fail to produce fever in the usual way in animals poisoned by curare (Reichert). Curare merely removes the nerve-control of muscles; it does not act on the tissue-substance or interfere with its metabolism in any way.

CHANGES IN FEVER.

Metabolic Changes.—There is increased oxidation in fever. The amounts of oxygen absorbed and CO_2 given off are both increased, although the relation between them ($\frac{\text{CO}_2}{\text{O}_2}$, or respiratory quotient) is practically unaltered. This indicates that, although the amount of combustion is increased, the substances oxidized are probably the same as in health under similar conditions of diet.

The amount of urea eliminated in fever is greatly in excess of the amount given off by a healthy person on the same diet; this indicates an increased destruction of proteids in the body. As the amount of nitrogen absorbed from the alimentary canal is less than the output in the urea, some of it comes from the permanent tissues of the body. This fact is also made known by the great emaciation seen in febrile patients. The fats likewise disappear from the tissues, the resulting metabolites being CO_2 and H_2O .

Uric acid is also increased, but is somewhat variable in amount. This results from the metabolism of nucleoproteids. The N of proteids is probably eliminated entirely as urea and has nothing to do with uric acid. The metabolic changes producing these two classes of materials are distinct, and each one is influenced by different conditions. Although there is generally a

fairly uniform proportion between the amounts of uric acid and urea in the urine, this is by no means constant. The amount of uric acid probably depends upon the degree of leukocytosis (or rather of leukocytolysis) more than upon any other factor. Even when there is no leukocytosis, there is some increase of uric acid, probably coming from the nuclei of the fixed tissues.

The increased oxidation is generally regarded as a part of the febrile process, and not the result of the high temperature. There seems to be no relation between the elevation of temperature and the amount of oxidation. It has been found in intermittent and in septic fevers that oxidation is increased before the rise of temperature begins, and rapidly reaches its maximum long before the temperature attains its height.

On the other hand, in thermic fever (Welch) and in purely nervous fever produced by cerebral puncture (Ott), there is increased oxidation in rabbits, as is evidenced by wasting of the tissues, although the animals eat greedily. The loss in weight is not due entirely to the loss of water. As the temperature is primarily affected in these latter conditions, we may conclude that the pyrexia may in part cause the increased metabolism, but is not the sole cause of it.

Functional Changes.—Circulation.—The pulse-rate is increased in fever; the increase being, on the average, 8 pulsations for each degree Centigrade or 4.5 for each degree Fahrenheit. While this acceleration, at least in the beginning, is brought about through the nerve-centers controlling the activity of the heart, there is also no doubt of the direct action of warmed blood upon the heart, as has been repeatedly demonstrated by perfusing the isolated mammalian heart. Although the systole is somewhat shortened, the increase in frequency is chiefly at the expense of the diastole or period of rest. When fever continues a long time, as typhoid fever, this may have considerable significance.

The blood-pressure is variable; although it may be increased early, it is nearly always diminished late in fever. The feeble, soft pulse in advanced stages probably indicates a combined condition of weak heart and lessened arterial tension. Welch found that blood-pressure in rabbits kept in a state of thermic fever for two weeks was normal, although there was moderate fatty degeneration of the myocardium. It is quite probable that the peripheral vessels are altered in fever, and this condition contributes in large part to the lessened pressure. Probably there are changes both in the cardiac and vasomotor nerve-centers, as well as in the organs controlled by them.

The dirotic pulse which occurs late in prolonged fevers indicates great alteration of vasomotor tone. That there are also changes in the blood-vessels before any decrease of pressure occurs is rendered probable from the way in which the vessels in the rabbit's ear or the cutaneous vessels of man react to stimulation which normally produces vasomotor changes. Changes in the blood-vessels seem to be due more to the poisons causing the fever than to the pyrexia alone.

Respiration is generally accelerated in normal proportion to the pulse. Although it may be shallow, the volume of air respired is increased. The frequency is not always in proportion to the temperature. Even in pneumonia, where the local conditions would be expected to determine the rate, the chief cause appears to be the toxemia. This is seen in the abrupt fall in the respiratory rate, with the crisis, before consolidation has disappeared.

Although warmed blood can produce acceleration of the respiration by acting directly on the respiratory centers, the pyrogenic agent probably acts in the same way.

Exposing a furred animal to hot air increases the respiratory rate enormously, as this is the only way these animals have of regulating their temperature. This condition is called "heat-dyspnea" by some, and "thermopolypnea" by others.

Secretions.—*Digestive Secretions.*—The saliva is diminished in amount, and the glands cannot be excited to increased activity reflexly as in health.

The gastric juice is decreased in amount, and there is a great reduction in HCl. Pepsin does not appear to be affected.

The bile is said to be diminished. These alterations of the digestive juices would account for the anorexia and enfeebled powers of digestion which occur in fevered patients. Absorption is also greatly delayed, and peristalsis is retarded.

Sweat is decreased in the early stage, and increased in the terminal stage. The hot, dry skin is no indication of the amount of sweat given off. W. Hale White found that it sometimes decreased in typhoid fever; but in other diseases (pneumonia and erysipelas), he found that it increased, even when the skin felt dry.

Renal Secretion.—The urine is increased in the cold stage of fever, from the internal congestion and increased blood-supply resulting from the peripheral vasoconstriction. During the hot stage the urine is decreased, because more water is lost through the skin and lungs than is normal. In the terminal stage the urine may become scanty, from the great increase in the loss of water by the skin.

Albuminuria seems to be due to changes in the kidney structure or function, and not to changes in the blood alone. It is not present in all fevers. When it occurs, it does not appear early when the temperature is at its height, but late, when the structural changes are most pronounced. It occurs most frequently in diseases causing pronounced structural alterations in the kidney, *e. g.*, diphtheria, yellow fever, etc.

Changes of the inorganic ingredients, *e. g.*, the increased elimination of phosphates and of potassium salts, the diminution of sodium salts and of chlorids, all result from altered metabolism in the tissues.

Nervous Symptoms.—Cerebral activity is generally dulled, but may be increased but perverted, *e. g.*, delirium, hallucinations. Whether this is due to pyrexia or to the material causing pyrexia, it is impossible to say at present.

Late in the course of prolonged fevers, incontinence of urine and of feces may occur from disturbance of the function in the centers of the spinal cord. Just what structural basis there is for such change of function cannot be stated, but such changes occur in the nerve-cells.

Blood.—All the changes in the blood are variable. The red corpuscles may be normal, increased, or decreased. The differences of distribution of the blood from vascular changes make blood-counts less accurate than in health. Sometimes there appears to be a real destruction of corpuscles. At other times, the seeming increase of corpuscles is only relative, due to increased loss of water from the body or to disturbed circulation.

In most fevers, there is more or less leukocytosis; and even when it does not occur, there is a change in the kind of leukocytes. The writer

found that pyrexia alone, produced by placing animals in a hot box, does not produce leukocytosis. The poison causing the fever is probably the cause of the leukocytosis.

The alkalinity of the blood has been found by some to be increased, and by others to be decreased. These deviations from the normal appear to result either from the direct changes of the pyrogenic agent or from the changes in metabolism. They do not occur in the pyrexia of nervous origin or in thermic fever; and further, the changes in alkalinity do not coincide with the pyrexia. It has been suggested that increase of alkalinity is a favorable sign, showing increased resistance on the part of the animal economy to the infection, while decreased alkalinity indicates the opposite condition.

Structural Changes.—Widespread degenerative changes are commonly found in the tissues after death from febrile diseases. This may be (*a*) parenchymatous degeneration or cloudy swelling, or (*b*) true fatty changes. The former is commonly regarded as a transitional stage of the latter; and the fact that cloudy swelling occurs in mild or rapidly fatal infections, while fatty degeneration only appears after a very severe or prolonged febrile process, lends plausibility to this view.

The tissues showing these changes are the liver, kidney, heart, and voluntary muscles, especially those continuously active in respiration, as the diaphragm.

Whether these degenerations occur as a result of the infection or of the pyrexial process has been the subject of considerable discussion. That the toxemia alone can produce profound changes is seen from the marked structural alterations found after acute infections where there has been little or no pyrexia, as often occurs in diphtheria, sometimes in septicemia, and occasionally in typhoid fever. This degeneration is not the same in all infections, but appears to depend chiefly on the kind and severity of the infection and not on the vigor of the pyrexial process.

On the other hand, pyrexia without any toxemia, produced by keeping rabbits in a hot box with an average rectal temperature of 41.1°C . (106°F .), will produce cloudy swelling and moderate fatty degeneration, if the pyrexia be maintained for at least a week (Welch). This is not constant, however, as Naunyn failed to find it after keeping rabbits in a hot box for two weeks. Welch also found that, the higher and less fluctuating the bodily temperature, the more certain is the degeneration to occur.

It would therefore appear that both factors contribute to the structural changes.

Just how closely these structural alterations are associated with disturbances of function, or to what degree they form a source of danger, cannot be positively stated. Clinicians may overestimate this relation, and pathologists may possibly underestimate it, especially in regard to the heart. In his experiments on rabbits, Welch found that, although they had been confined in a hot box for ten days or two weeks, until the heart showed well-marked fatty degeneration, the normal blood-pressure was maintained and the heart responded to stimulation of the vagus in the usual way. In other words, after pyrexia without toxemia, the structural changes did not prevent the heart from acting in a perfectly normal way, to all appearances.

The weak pulse and feeble first heart-sound observed clinically after severe infections, as well as an occasional sudden death from true heart-

failure, indicate that the changes after toxemia are usually much more severe and the interference with function more serious.

Since the method of staining the neurones of the nervous system by silver impregnation has been used so extensively, profound changes of these cells have been found in at least two infections—tetanus and diphtheria. These consist in a loss of the gemmulæ, great varicosity of the dendrites, and shrinkage of these processes of the cell. More extended observations are needed in other infections and in nontoxemic pyrexia. The meaning of these changes of structure in the neurones is still a matter of controversy, but it is highly improbable that such striking changes as occur in the above-mentioned infections are artefacts or normal variations, although some very slight changes attributed to the influence of some drugs may be such.

THE SIGNIFICANCE OF FEVER.

The real significance of fever has been a matter of much speculation and difference of opinion. Until recent years the opinion has prevailed that the chief source of danger and the main point to be combated by treatment is the elevation of temperature. It is true that high fever which is uncontrollable and does not respond to the usual methods of reducing temperature is of grave significance, not merely from the pyrexia itself, but because it is an indication of the severity of the disease.

Of late years, however, opinion has changed greatly; and the view that fever, or at least a moderate degree of fever, is beneficial rather than harmful, and is Nature's way of defending the organism against the infection, is being more generally accepted. While there may be danger of this idea being carried too far in the treatment of fevers, there can be no doubt that many infections, such as typhoid fever, pneumonia, and sepsis, seem to do better and the prognosis is more favorable when the animal economy responds with a positive but controllable pyrexial process than when there is very little febrile reaction. Cases of otherwise apparently moderate severity, without such a febrile reaction on the part of the patient, often do badly or terminate unfavorably.

Bacteriology has perhaps produced the strongest evidence causing this widespread and radical change of belief as to the nature of fever.

It is a well-known fact that the *Micrococcus lanceolatus*, the *Bacillus anthracis*, and the *Bacillus tuberculosis* thrive best at the bodily temperature, and do not develop in the usual way at 42° C. Indeed, the virulence of the first two is distinctly lessened from exposure to this temperature.

Ordinarily fowls are not susceptible to anthrax; but it has been found that, if their temperature be reduced in various ways, they become infected and succumb to the disease.

Further, rabbits kept in a warm chamber at 40–42° C. are able to resist infection with the pneumococcus, but become infected when taken out. Control animals at the room-temperature perish in a short time when inoculated with the same organism (Walther).

Cooling rabbits artificially increases their susceptibility to the pneumococcus, and they perish before others kept as controls at room-temperature. Similarly artificial elevation of bodily temperature by keeping rabbits in a hot box prolongs life after infection with anthrax and rabbit septicemia, while lowering their temperature in the same way shortens it (Rovighi).

So, also, Filehne demonstrated that rabbits infected with erysipelas in the ear show a rapid reaction of short duration, with speedy recovery, when kept in a warm chamber; while others infected in the same way at the room-temperature show a much more severe reaction, which lasts a long time, and they recover very slowly.

In the same way, rabbits with fever produced by cerebral puncture are able to live longer after infection with chicken-cholera, pneumonia, and swine-erysipelas than controls; they are able to resist an amount of toxin several times as great as that required to kill animals under ordinary conditions; the local reaction with erysipelas may be severe, but terminates in recovery (Löwy and Richter).

These experiments indicate that *the real danger in fever is not the pyrexia or elevation of temperature, but the poison causing it*; and that fever is, in a measure, like inflammation, a beneficial process, operating to protect the economy.

TERATOLOGY.

CLASSIFICATION.

TERATOLOGY treats of deviations from the normal in the development of the embryo. In a broad sense it treats of all malformations or anomalies of animal structure, from a slight variation like an anomalous artery, through the supernumerary digits, the meningoceles, the brainless monsters, the acardiac and amorphous fetuses, to the double and triple monsters. The word teratology is derived from the Greek *teras*, the equivalent of the Latin *monstrum*, meaning portent. The birth of a monster was anciently considered an omen of woe and portentous of calamity.

A satisfactory classification, in the present state of our knowledge, cannot be made. It is not yet possible to divide all malformations into classes according to etiology alone, although the best attempts are along that line. The early classifications were according to external appearances and dissection. Buffon, one hundred years ago, suggested dividing human malformations into those by excess, those by defect, and those by altered form. This classification, however, is incongruous, throwing together such widely different conditions as supernumerary digits, giants and double monsters, hypospadias, dwarfs, and acephali. Vrolik declared that classification was not possible beyond the merest convenience in grouping.

An article on teratology would be incomplete without some consideration of the system of classification elaborated by St. Hilaire in the third decade of the nineteenth century. His scheme was based upon external shape; and, since malformations allied as to external shape have often a similar etiology, a classification based upon such characteristics is not entirely unscientific. His plan is the basis of all later ones and is still extensively followed in teratologic literature. According to his scheme, all vertebrate malformations can be embraced in four great divisions: *Hemiteratic*, *heterotaxic*, *hermaphroditic*, and *monstrous*.

The **hemiterata** include all anomalies of structure not of the specific character of the hermaphroditic or heterotaxic malformations, nor yet grave enough to be classed with the monsters. Of course, here, as elsewhere in natural science, dividing lines are indefinite. The line between anomalies such as the hemiterata and true monsters may be roughly determined by the consideration whether the malformation is compatible with a continued existence of the affected individual in a manner not essentially different from that of his fellows. Thus, a man with digits deficient in number might live a life nearly normal, while one having the shortened limbs of a phocomelus could fill only a very restricted scope of existence. Among the hemiterata are the anomalies of volume, as dwarfism and giantism, of local smallness or bigness; anomalies of form, as crooked noses or the congenital deformities of the pelvis; anomalies of color, as albinism or melanism; anomalies of structure, as defective or excessive calcification of bones;

anomalies of disposition of organs, such as herniæ, club-foot, aberrant blood-vessels or muscles, imperforate canals, unclosed clefts like harelip; anomalies of number, as supernumerary breasts or defective number of digits or the existence of a tail, which last means merely an excessive number of coccygeal vertebrae.

Heterotaxis embraces all cases of inversion of organs or parts of the body. There may be a complete *situs inversus viscerum*—that is, a condition in which all the organs are transposed as to the sides of the body; or there may be a less general transposition, involving only the situation of the heart on the right side, the liver on the left, or a wrong-sided position of one or more organs. Usually more than one organ is involved, and more often in the abdomen than elsewhere. With visceral transposition there does not necessarily or even usually exist also lefthandedness. Transposition will be considered further in connection with homologous twins.

Hermaphroditism includes all the varieties of amphimorphism of the external and internal genitalia.

Monsters are of course the most numerous and interesting division in St. Hilaire's system. He classifies them according to external form and is needlessly explicit in his fine distinctions, but in the main his grouping is convenient. He has at least given us a useful working terminology which even to-day can be followed with advantage.

The classification of Ahlfeld, which will be followed in the main, retains much of that of St. Hilaire, but arranges the different orders and species more according to their proved or probable causes. He first considers splitting of the undifferentiated embryo, resulting in composite monsters, double or triple. In the first division of this order are included cases of complete splitting, the homologous or uniovular twins (and triplets), the allantoic and included parasites, and twins joined at the thorax, umbilicus, or cranium. In the second division of the order of double monsters he includes those in which the duplicity is only partial, involving only a portion of the cerebrospinal axis; such are the dipygi, syncephali, ischiopagi, pygopagi, and rhachipagi. The other order includes all the single monsters and anomalies. The first division embraces those anomalies and monstrosities due to the splitting of the embryonal area of single parts, members, or organs, producing supernumerary or accessory parts. Another division includes those anomalies due to nonclosure of the anterior and posterior commissures of the body, a numerous and well-marked class. Lastly there are various small classes not included in the foregoing and due to causes sometimes undetermined.

TERATOGENESIS.

Teratogenesis, or the theories of the origin of anomalies, malformations, and monsters, may be classed as superstitious and scientific. We should like to be able to say that the theories of the former category belong entirely to the dark ages of medicine and to the period before the revival of letters. It is astonishing to note, however, that some are held even to-day by medical men. One reason why we find so few recorded cases of monsters in the classical literature is because such infants were almost invariably destroyed at birth, being considered evidences of the wrath of the gods. In the Middle Ages, Satanic influence, either by direct cohabitation or indirectly, was thought

to be a frequent cause of monstrosities. Sometimes, especially when in the eyes of witnesses the monster very strongly resembled an animal, bestiality on the part of the woman was made to account for the case. In Copenhagen, in the sixteenth century, a girl was burned at the stake for bearing a fetus which resembled a dog, probably an anencephalus. The superstitious element is still seen in the present common law, by which a monster may inherit if it resembles the human form, and not inherit if it resembles a beast.

The superstitious idea as to the causation of monsters which has resisted the influence of reason the longest, and which is still held by perhaps the majority of medical men in this country, as well as almost every layman everywhere, is that nervous or mental impressions of the mother, occurring during pregnancy, in some mysterious manner react upon the growing embryo so as to cause it to undergo some kind of malformation.

Not only monsters, but even the common pigmented spots, moles, and nevi, are popularly supposed to be the results of maternal marking. The course of reasoning usually is that first the anomaly is observed, and then something is sought in the history of the pregnancy to which the anomaly may be ascribed. Great ingenuity is often displayed in ferreting out some fright or mental shock as the cause of the phenomenon. Since anencephali are by far the most common of monsters, and since, from the lack of cranium, their foreheads recede abruptly above the eyes, thus giving the appearance of the head of some animal, like a dog, cat, or frog, it is usual to find in the history of the case that the mother was frightened or shocked by seeing such an animal under frightful circumstances. The literature is full of reports of cases in which maternal impressions were supposed to have caused anomalies, but the maxim *post hoc ergo propter hoc* applies in nearly all. The time in the pregnancy seems to be immaterial; the same sort of malformation is often reported to have been caused in different cases at various periods of gestation. The arguments in favor of the influence of maternal impressions rest entirely upon the fact that in a large number of cases anomalies have followed nervous shocks inflicted during pregnancy, or that, after the birth of a fetus abnormal in some particular, it has been possible to discover a story of such shock. No experiments have ever been recorded by competent observers.

In the first place, the theory of maternal impressions should explain all cases. In most, in spite of diligent search, no event can be found to account for the particular anomaly under consideration. Conversely all cases of fright or nervous shock during pregnancy should be followed by the birth of a monster, or at least of an anomalous fetus. Comparatively few women go to term without at some time having had a mental shock or fright as great as many of those reported as producing abnormal fetuses, but monsters and anomalies are comparatively rare in the number of children daily brought to the light. How also shall anomalies be accounted for in internal organs, of the existence of which the mother perhaps did not know? Most malformations involve either an excess or a deficiency of tissue. It is hardly conceivable that a mental impression of the mother could remove structures already formed. Thus, the sight of a one-eyed man at the middle of pregnancy could hardly cause one of the eyes already formed to disappear, leaving only one, and that in the middle of the forehead, as in Cyclops. Yet we know that the eye-vesicles begin to bud out from the cerebral vesicles, one on each side, during the first fortnight. So in most malformations the organ

or part under attention is usually far on in its development and beyond the reach of any deterring influence during the early weeks or even days of gestation, while most of the recorded maternal impressions occur late in pregnancy. If it is hard to conceive how the mental condition of the mother could remove any part of the embryo, it is even less conceivable how it can add anything. How can the redundant anomalies, the supernumerary organs or digits, and especially the double monsters, be accounted for by the theory of maternal impressions?

The mammalian or even the human ovum, except for nutrition, is really as much outside of the influence of the mother's body from the moment of its escape from the ovary as is the egg of fowl or fish. The placental villi commingle with the greatest intimacy with the glandular tissues of the uterus, but at no time or place does the maternal tissue coalesce with that of the fetus, nor even does the mother's blood reach the veins of the offspring. Even supposing that nervous stimuli could pass from uterus to placenta, how could they reach the fetus through the umbilical cord, which is known to be devoid of nerve-fibers?

Numerous experiments have been performed upon the eggs of birds and lower animals, which have resulted in producing all the typical varieties of monsters, especially the single ones. Malformations are artificially produced in the embryos of birds, identical with those in man that have been ascribed to the influence of maternal impressions. As we shall see in considering the etiology of different malformations, most of them can be ascribed to perfectly definite physical and mechanic causes entirely dissociated from psychic influence.

For almost all forms of anomaly or monstrosity a scientific cause has been found, and for those still undetermined there is reason to believe that a rational cause will at some time be found. The occurrence of malformations can be explained mostly by the action of physical forces external to the embryo. Double formations arise from fission of the whole or a part of the original embryonic cell-mass. This fission occurs either from a superabundance of germinal material in the original embryonic area, or from constriction upon the embryo by the zona pellucida, or upon a combination of both causes. The action of abnormal amniotic bands and the adhesions of the overlying amnion to different parts of the embryo are potent factors in the production of single monstrosities. In the amnion we have a membrane resembling peritoneum and doubtless subject to the effects of irritation, inflammation, and vascular changes that would cause more or less cicatricial contraction and more or less adhesion of different parts of the membrane to other parts or to the surface of the embryo underneath. Occurring at different periods of the embryonic development, these abnormalities of the amnion give rise to vastly different results in the final outcome of the monstrosity. Folds or bands lying within clefts and openings which normally close at a later period may cause various abnormalities from incomplete closure at the proper time or at all. That such amniotic bands and adhesions are seldom seen at the birth of the fetus is weak argument against their former existence, because such is the developing and restorative power of embryonic tissue that it is very easy for the amniotic cause to have disappeared, although leaving a monstrous condition in the fetus as a result of its former presence. We may speak with truth of arrested development as a frequent cause of fetal anomalies. We must remember, however, that the

cause of this arrested development itself is some mechanic hindrance to the ordinary course of embryonic life. This mechanic hindrance is usually found in amniotic bands or adhesions. Some are due to circulatory disturbances or other factors that cause dropsic enlargement of internal organs, such as the brain or abdominal viscera, and consequent nonclosure of the dorsal or ventral commissure of the body. There still remain some abnormalities which must be ascribed to arrested development alone, because the ultimate cause of the arrest cannot be determined. Atavism has been invoked to explain some few anomalies: such, for instance, as the existence of a tail, an excessively large appendix vermiformis, and perhaps supernumerary digits. The presence of a caudal appendage is probably the result of persistence of an embryonal structure.

DESCRIPTION OF VARIETIES.

Compound monsters are those in which there are present to a greater or less degree the parts or organs of more than one individual. Since there is only one perfectly authentic case on record of a monster more than double, it will be sufficient to consider compound monsters as merely double. There is always regularity in the direction and extent of the duplicity. There is never, for instance, a head at each end of the body, an extra limb growing from the occiput, or other such irregular junction of parts of two individuals. The cerebrospinal axes are always more or less divided; that is to say, there is always an approach to two individuals with axes originally parallel. The evidence of duplicity may be very slight, involving only the extreme anterior portion of the face or the tip of the tail, but always a portion of the cerebrospinal axis. Externally it may appear as if only the tip of the tongue were double; but, to be a true compound monster, there must be also a trace of duplicity in the bones of the base of the skull.

It was formerly considered that double monsters were due to the junction of two fetuses lying close together. This would be impossible with twins from two eggs. The chorions and amnions of the ova would prevent union; even if these membranes should coalesce, the presence of the amniotic fluid and the motions of the uterus and of the embryos within it would effectually prevent junction of the twins. Double monsters, the individuals of which differed in sex, have never been authentically recorded. If coalescence of biovular twins were possible, double monsters having one part male and the other part female would sometimes be observed. The fact that double embryos are always joined at identical parts is proof that they were not due to junction of two previously separate fetuses, because then the two embryos would sometimes be joined irregularly, such as head end to tail end, abdomen to dorsum, upside down, and the like. Such double monsters are never seen, although it may at first sight seem so in some instances of parasitic forms.

Though coalescence of biovular twins is almost universally denied, yet the possibility of the origin of compound monsters from so-called double-yolked eggs must be considered. In birds' double-yolked eggs, hatching sometimes occurs; although rarely are two embryos formed, and never double monsters. There is no ground for believing in the existence of an *ovum in ovo* among mammals. A double-yolked egg of a bird merely means

that two yolks, which alone are the analogues of the mammalian ova, have entered the oviduct close together and have become enveloped together in the white membranes and shell. An avian double-yolked egg is essentially two ova, and cannot be compared to any condition obtaining among mammals. Authorities are nearly unanimous in holding that all double formations arise from one ovum.

Assuming, then, that only one ovum is concerned in the formation of double monsters, we are confronted by two theories as to their formation from the one egg. One holds that they arise from splitting of the germinal area of one embryo, and the other that they arise from the fusion more or less of two distinct embryonic areas lying in one ovum. These are the fission theory and the union theory. By the former the embryos are supposed to have been originally one, and to have split into the parts of two embryonic areas; by the latter they are supposed to have been double from the beginning, and to have become more or less joined together. It is certain at least that the fission or the union of the embryonic area or areas takes place at a very early period, long before any differentiation of the cell-mass has begun. In the bird's egg this is probably before the egg has been laid. While the question is still far from determined, and while either solution will give a working basis for classification, yet the largest number of the best authorities favor the fission theory. The advocates of the union theory claim that the circumstance whether the blastoderms lie near or far from each other on the surface of the ovum determines the union or the complete independence of two embryos. The first would claim, for instance, that homologous twins arise from a complete splitting of the embryonic cell-mass; while the second would claim that the diprosopi or the double-tailed monsters arise from a complete fusion of the embryonic cell-masses of a pair of homologous twins.

All uniovular twins and the two halves of double monsters are usually very much alike—physically, mentally, and morally. The fission theory explains all the varieties of double formations, from homologous twins to duplex digits. The amniotic fold which was the cause of the fission of the anlage of a duplex thumb has been found persisting between the portions of the duplex digit. A strong point in favor of the fission theory is that the union is always, even in parasitic cases, at an identical point in each portion of the monster. Except in the cases of included fetuses, the union is always by the longitudinal axis of the body, and the poles of the two portions of the monster correspond. Again, the anterior or cephalic end is the larger in the embryo; and therefore, if two embryos unite, we should expect that end—approaching, on account of its size, nearer to its twin—to be more frequently united with the latter. On the contrary, the union is more often at the caudal end. Observation and experiment are limited in respect to beginnings, in the history of double monsters. The earliest double human embryo is of four weeks' growth, and the earliest double hen embryo twenty-four hours; both too old to allow study of the formation of the double germs. This is best studied in the eggs of fishes, amphibians, and echinoderms, which lend themselves more readily to observation and experiment.

Twin births, to a certain extent, run in families. It seems as if the eggs of certain women had an excessive amount of embryonic material, or that such women produced more eggs. The author has personal knowledge of a woman who has produced two pairs of apparently uniovular twins. It seems that

for homologous twins and double monsters there must be at a given period an excess of constructive material over that required for the same period in a single embryo. Polyspermia, the condition of two spermatozoa gaining entrance to one ovum, might perhaps be thought to influence the production of double embryos. While it is possible for two spermatozoa to enter one ovum and even go so far as to produce two male pronuclei, yet such polyspermious eggs whenever observed always blast very soon afterward, even before the segmenting stage. Such observations have been made and controlled experimentally in the eggs of frogs and fishes.

Although double-yolked eggs in the true sense cannot exist in mammals, yet binuclear and polynuclear eggs have been considered evidence in favor of the union theory. These so-called twin eggs have long been observed in the primary follicles of the ovaries of mammals and even of the human species. Although segmentation of the primordial ova of man had been denied, yet Schultze saw, in a four months' embryo, marked increase of these ova through mitosis. Double-egged primary follicles have been observed by others, and also double-nucleated eggs in the newborn and even in children of few years. Nagel takes these to be true twin eggs and considers that twin embryos may develop from such. Up to 1899 the oldest girl in whom polynuclear eggs had been observed was four years of age. Von Franqué reports that he has seen, in the ovary of a girl of fourteen years, numerous primordial eggs with two, and one with three, nuclei. Also, he is the first to report the existence of a binuclear ovum in the ovary of an adult woman. The ovaries of a woman of thirty-five were removed for cystomas. In one ovary he found a follicle containing an egg which had two nuclei, each containing a germinal spot or nucleolus. The egg appeared normal in structure and development. He concludes that this was a true twin egg and that from such are developed uniovular twins.

Of course the latter conclusion does not necessarily follow. In the first place, it is not certain that the embryo develops from the nucleus or so-called germinal vesicle. All we know is that the male pronucleus derived from the spermatozoon approaches, within the ovum, and joins the female pronucleus, which is not proved to be identical with the germinal vesicle. Even were it so, still it is not proved that the spermatozoon divides to fertilize both female pronuclei, or that two spermatozoa enter double-nucleated eggs. So far, only one observation has been made of a polynuclear ovum in an adult, and yet we know that uniovular twins are relatively not rare. It is perfectly reasonable to conclude that double nuclei in the ova of mammals merely mean the segmenting and consequent increase of ova. If double-nucleated or so-called twin eggs develop usually into uniovular twins, we should expect, on account of the relative frequency of the latter, that such eggs would be found with equal frequency in the ovaries of adult women.

If further observation shall disclose that the occurrence of binuclear ova in the ovaries of sexually mature women is relatively as common as the occurrence of uniovular twins, or if observation proves that a double embryo or two embryos have developed from such an egg, it will be necessary to believe that from such twin eggs may arise homologous twins and double monsters. All appearances indicate that these double embryos and twin embryos arise in eggs which have a superabundance of formative material. Prolific women are more apt to bear homologous twins, and it may be that the primordial ova of such women have segmented and increased more than

commonly, so that there is an excessive amount of nuclear material in the ova, even to the extent of the existence in some ova of two nuclei. Perhaps the female pronucleus is formed in these twin eggs from the two nuclei or germinal vesicles, and therefore becomes unduly large, so that in the embryo an excessive amount of embryonic material is provided, which gives rise to two embryos or to a double embryo.

That fission of the embryo is possible from mechanic force has been

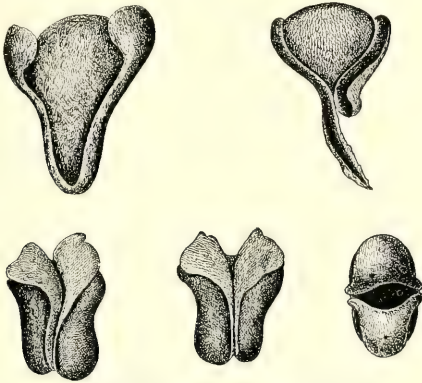


FIG. 139.—Duplex formation in frogs (O. Schultze).

proved by O. Schultze's experiments on frogs' eggs (Fig. 139). He produced double monsters by holding eggs between glass plates and turning them at different angles during the segmentation stage. Fish eggs carried far in railroad-cars and other vehicles, and thereby subjected to considerable shaking, show a much greater percentage of double formations than eggs hatched without such agitation. It has also been found that more double monsters develop from fish eggs hatched in running water than from eggs of the same species and under similar circumstances hatched in still water. Various mechanic causes may act in producing the very early splitting of the embryo so that a double monster is produced.

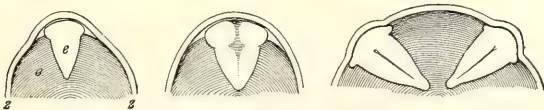


FIG. 140.—o, Blastodermic vesicle; e, Primitive germ; z, Zona pellucida (Ahlfeld).

In mammals the splitting of the embryo is probably very often due to constriction of the zona pellucida upon the embryo underneath (Fig. 140). There is perhaps a disproportion between the germ and the zona pellucida. Perhaps the excessive amount of the embryonic material causes the cell-mass to project unduly above the surface of the ovum. This causes the zona pellucida to be stretched more or less tightly over the germ, and there-

fore to cut through the cell-mass of the underlying embryo. This occurs at a very early period, even before the formation of the primitive groove. In fact, this splitting of the embryonal anlage takes place before the cells have been at all differentiated, shortly after the completion of segmentation. Then, either because there is excessive amount of embryonic material in the embryonal anlage or because the zona pellucida is unduly small, there ensue a pressure and a stretching of the enveloping membrane, which gradually cuts into the embryonal mass, causing it to develop doubly, in whole or in part, according to the extent, direction, and situation of the splitting.

If the fission has been complete, the two halves will lie parallel and will slip down on the blastoderm away from each other, while the yolk-granules from below are forced upward between the two embryos. If the fission has been only partial, then the split portions will slide down the blastoderm and be separated by the yolk-granules, while the united portion remains in its former situation. In all double formations and homologous twins, the sex is female twice out of three times, but always identical in both portions.

The most probable cause, then, of double monsters is splitting of the very early embryo into two parts, partially or wholly separated. They arise from one ovum and from one impregnation. Their classification is based upon the extent and direction of the splitting.

Homologous Twins.—When the splitting or the separation of the undifferentiated embryonal anlage is complete and the two portions of the embryo go on to perfect development, there are born the so-called homologous or uniovular twins. While, in the autositic stage they can hardly be called monsters, and would probably themselves resent that title, yet their mode of origin is doubtless the same in kind as that of true double monsters. Uniovular twins are always of the same sex and are always much more alike in bodily appearance, mental characteristics, and even moral nature, than are biovular twins. Of course, the resemblances are most marked at birth and in very early childhood. After they go about separately in the world and are subjected to different environment, each acquires peculiarities of his own; but throughout life, and even to advanced age, there persists a remarkable unanimity of appearance and thought. Homologous twins are not rare. Of 506 twin births examined as to the membranes, 444 were proved to be double-egged and 62 single-egged; therefore, one twin birth in seven is uniovular. Twin births in general occur about once in 100 labors; therefore uniovular twin births occur once in 700 labors.

Uniovular twins can be recognized at birth by the existence of but one chorion. There is almost always only one placental mass, and the allantoic vessels usually anastomose more or less with those of the fellow-twin. This anastomosis is sometimes a serious or even fatal matter to one of the twins. Homologous twins are very likely to have the same diseases and especially the same congenital anomalies. The latter phenomenon may be explained by the fact that they usually occupy the same fetal membranes and so are subject to the same results of diseases of these membranes. Thus, if spina bifida or nonclosure of the abdomen occur in one, it is likely to occur also in the other.

Parasitism in Homologous Twins; Acardiacus.—We have so far considered the autositic uniovular twins; in other words, those of development equal throughout gestation. Their parasitic varieties occupy the realm of

real monsters. Up to about the twelfth day, the two embryos develop evenly. At that time the allantois buds out from the hind gut of each individual, and its vessels reach the placental portion of the chorion. Sometimes the allantoic vessels and later the placental vessels anastomose too freely with those of the other twin; then begins a contest of the two fetal hearts, as to which shall dominate the circulation. One fetus, from its more favorable situation or other cause, overcomes the force of the other's heart in the anastomosing vessels, and thereby is caused a stasis in the arteries of the weaker fetus, progressing inward from the anastomosing allantoic arteries. Finally the force of blood-circulation is entirely overcome in the body of the weaker fetus, and it dies. The increasing growth of the surviving twin with its appendages gradually compresses the dead one and finally squeezes it flat against the uterine wall, so that the *fetus papyraceus* results. Other causes of the early death of one twin may also bring about such a deformed fetus. The twins are not necessarily homologous, but the foregoing is by far the usual process in the production of the flattened fetuses. Unless careful search is made among the membranes and clots, such flattened fetuses, especially if the death occurred early, may be overlooked at the birth of the live one (see transposition of viscera in homologous twins).

The true allantoic parasites arise in a similar manner. Two healthy

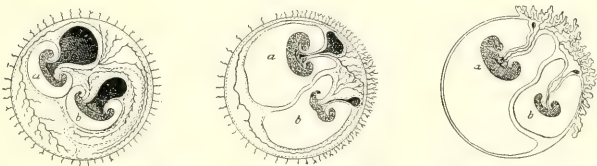


FIG. 141.—Schematic representation of the development of the pure allantoic parasites (Ahlfeldt).

embryos develop from one egg, as in ordinary cases of homologous twins (Fig. 141). The allantoic stalk of one may reach the inner surface of the primary chorion a few hours or so before that of the other. It becomes attached to the chorion here and begins to develop its umbilical vessels before the second allantois reaches the placental site. Therefore the allantois of the second embryo finds no chorionic attachment or only a limited one, and is compelled to attach itself to the allantois of the first. There results an anastomosis of the umbilical vessels, and the first fetus becomes dominant in the circulation. As the allantoic stalks become lengthened out into umbilical cords, the cord of the second may be attached to that of the first at some distance from the placenta; it may be attached to the placenta close to that of the first, or the two may be connected by a large vessel upon the placenta. The anastomosing arteries leading to the second will carry all or nearly all of the blood directly from the circulatory system of the first, without going through the placenta. The venous current, being slower, will not follow the line of least resistance so markedly. The second embryo, therefore, gets arterial blood—that is, vitiated blood—from the first embryo's body. Also the blood-pressure from the heart of the first forces the current backward through the arteries of the second. The embryonic heart of the latter atrophies. The current is more direct from the umbilical arteries

toward the lower parts of the fetus by way of the hypogastric arteries than toward the head; in fact, the hypogastric arteries become the important vessels of the parasitic fetus. The organs normally receiving blood direct from the heart, such as the lungs, head, liver, etc., become atrophied or fail to develop at all. The distance from the heart of the autosite, which is the only pumping force in the bodies of both fetuses, is great; therefore the circulation is weak in the parasite's vascular system. On account especially of the stasis in the veins, there is usually a hypertrophy of the connective tissue, especially of the skin, and a general edema of the subcutaneous cellular tissue. According to the degree of the development of the



FIG. 142.—*Acepheus acardiacus dipus*.

allantois and placenta of the second embryo, we get several varieties in acardiac fetuses.

Acardiacus anceps is the least atrophied form, and is characterized by absence or nondevelopment of the face, the extreme anterior part of the body. There are rudiments of cranial bones and of the brain. The species is rare.

The most common species is the *Acardiacus acephalus*, in which the whole head is wanting or very rudimentary (Fig. 142). Sometimes there is found a little rudiment of cranium, and often a few hairs are seen upon the extreme cephalic end. Dissection usually shows the intestines and abdominal organs rudimentary, and the organs above the diaphragm are represented by the merest trace. There are rarely more than a few vertebræ,

and these are usually of the lumbar or sacral type; the shoulder-girdle is undeveloped, but the pelvic bones and those of the lower extremities are more nearly perfect.

The least developed form of acardiac monster is the *Acardiacus amorphus* or *anideus*, which is little more than a lump of connective tissue covered by edematous skin, sometimes bearing a few hairs. There is usually some attempt at budding-out of limbs, but these seldom have any systematic bony structure. A few pieces of bone may be found inside the body, and there may be some rudiments of visceral tissue.

The rarest acardiac monster, and indeed the rarest of all monsters, is the *Acardiacus acornus*, a fetus with head alone. Even the head is never fully developed, usually lacking some portion of the cranium and much of the brain. The genesis of this form of monster is very obscure, but the anastomosis of the yolk-vessels at the lower surface of the embryonic heart might account for the development of the head while the rest of the body remained undeveloped from malnutrition. The only representative of the body is a sac under the head, closing off the neck. In no case has an acornus been known to have an umbilical cord, but the head hangs to the placenta of the normal twin by means of the membranes. There is not sufficient evidence to judge whether or not the monstrosity is due to persistence of the vitelline circulation.

The *included fetuses* are the second class of parasitic twins. In some cases they may be due to attachment of the delayed allantois—not to the allantois of the autosite, but to some part of its body—and final partial or complete inclusion of such parasite within the body of the host. There is no umbilical cord running to such parasites, and they receive their nutrition from the anastomosing vessels of their hosts. The type of such fetuses is illustrated by the *Epignathus*, which is an acardiac amorphus which is joined to the autosite at the mouth, usually at the hard palate. It may be only a small tumor in the roof of the mouth or a huge pedunculated mass hanging out of that cavity. It is composed of numerous cysts which contain mucoid matter and sometimes brain-tissue, also rudiments of limbs and various organs. The epignathus arises because one of a pair of homologous twins is smaller than the other and lies near the head end of the larger twin. As the cephalic fold of the amnion of the autosite is folded downward as the head bends down, it carries with it, lying on the surface of the ovum in the near neighborhood, the whole of the smaller embryo, which thus becomes folded into the oral cavity or pharynx of the host (Fig. 143). Why one of the twins is smaller than the other can only be conjectured; perhaps, at the time it split off from the rest of the undifferentiated anlage, it was only a small portion of the mass. In the eggs of frogs it has been observed that small pieces of the egg will sometimes segment and develop like the larger part, differing only in size from the other embryo. It is conceivable that a minute por-

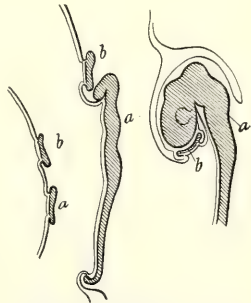


FIG. 143.—The inclusion of one embryo within the cephalic fold of the other (Ahlfeld).

tion of the undifferentiated cellular mass was pinched off by the overlying zona pellucida and detached from the larger twin-mass, afterward becoming included as above described. In a similar manner a smaller embryo may be included in the sacral region of the large twin, or in the abdomen or other part of its body where included fetuses have been found. The theories as to the origin of dermoid cysts and teratomas are discussed in another part of this work.

Double Monsters.—When the splitting of the embryonal cell-mass has not been complete, as in homologous twins—or, if we accept the union theory, when two embryos lying upon the same blastocele coalesce in part—we have the formation of double monsters in the restricted sense. These may be conveniently divided, according to the extent and direction of the duplicity, into Katadidyma, Anadidyma, and Anakatadidyma.

Katadidyma.—The *Terata katadidyma* are characterized by duplicity extending from the cephalic toward the caudal end, or, speaking of the human fetus, from above downward. This duplicity has all the grades, from the slightest, where there is little more than a double tongue, to the greatest, where there are almost two distinct individuals joined only by the nates and the tip of the coccyx. The Katadidyma may profitably be divided into four genera, according to the extent of the duplicity.

Diprosopus.—This genus is distinguished by a body apparently single and a head single caudally but more or less double as regards the face. A double tongue would hardly be considered to mark duplicity; but if on dissection



FIG. 144.—Dicephalus.

there is found a double condition of the anterior cranial bones, such would be considered the case. In some diprosopi the facial axes are nearly parallel, in some convergent below, and in some convergent above. The genus is divided into species, according to the number of eyes and of ears: in other words, according to the extent of the split; because the more extensive that is, the more room there is for eyes and ears. Therefore diprosopi are distinguished as *diophthalmus*, *triophthalmus*, *triotus*, etc. A constant characteristic is the existence of a single neck, because the duplicity does not extend below the cranium.

Diprosopus is relatively rare in man, occurring in about 6 per cent. of double monsters. The sex is female two-thirds of the times. It is most common in calves and kit-

tens. In a large number of human cases, anencephalus exists also. Partly because of this, and also because of the necessary defectiveness of the brain and the mouth which interferes with nutrition, these monsters are seldom capable of independent existence, though viable cases are on record. I have seen a case in an adult cow.

Dicephalus.—This form is characterized by the existence of two distinct heads with some splitting of the cervical spine even in the slightest cases. The genus is divided into species, according as the divergence of the spinal column is great enough to allow the development of two, three, or four arms, or of a third leg. Thus the species are called *Dicephalus dibrachius*, *tribrachius*, and *tetrabrachius*; also *Tribrachius tripus* and *Tetrabrachius tripus*. In all double monsters, as a rule, and especially in dicephali, there is a right and left symmetry of the internal viscera as far as the duplicity extends.

The two-armed species has only one thorax and abdomen and one shoulder-girdle; one heart (sometimes partly duplex); one pair of lungs (sometimes ateleatic rudiments between the normal ones); usually two stomachs and two gullets, but a duodenum which unites before the middle of its course. Where the separation is greater, as in the three-armed and four-armed species, there are two sets of ribs, with a sternum posteriorly, half of which belongs to each head. The greater the separation, the more likelihood that there will be two hearts or a heart markedly duplex. There is a common pericardium.

A famous case of *Dicephalus tetrabrachius dipus* was born in Sardinia in 1829, and was baptized Ritta-Christina. The fetus presented by the heads, which were delivered one after the other without much difficulty. The heads, arms, and upper portion of each thorax, to a point a little below the mammae, were separate and normal. The ventral surfaces were directed somewhat toward each other. If the right leg was pinched, only Ritta felt it, and Christina alone felt a pinch on the left; while at points near the median line, such as the abdomen, anus, and genitals, the sensations were common to both. The two heads cried and laughed, ate and slept, often at different times. Ritta caught a bad cold from which she never recovered, and died at the age of seven months. Christina, who had been sleeping peacefully for some time before her sister's death, suddenly sighed deeply and expired without warning. The autopsy showed only a rectum filled with feces and slight inflammation of the lungs of Ritta. It was found that her heart was compressed by that of her sister, and that fact probably accounted for her succumbing to a slight obstruction in rectum and lungs. Both hearts, which were rights and lefts, lay in the same pericardium, and in life beat synchronously. When that of Ritta stopped beating, that of her sister was of course interfered with and stopped. In double monsters, each part dies within a short time of the other.

Dicephalus is the commonest double monster in mammals, but is rarer in birds. In man, one-third of all double fetuses are dicephali. The sex is female twice out of three times.

Ischiopagus.—The distinctive feature of this genus is the existence of two bodies, with the pelves united in such a way that the pubes of one joins the pubes of the other in the median line. The bodies are separate above the navel, thus allowing two abdomens and two thoraces. The species is distinguished by the number of legs—two, three, or four. There are also various asymmetric and parasitic forms. The typical form, *Ischiopagus tetrapus*, contains the whole of two individuals united as to their pelves. If split through the pubes and separated, and the pubic regions united each to its own, two complete individuals would be formed. The union is typically at the tips of the coccyges. It is usual to have some malforma-

tion of the external genitals and atresia of one or both of the rectal openings. For this reason and because they are commonly born prematurely, it is rare for ischiopagi to live more than a few days. None are reported living more than one year. The monstrosity is much less common than dicephalus. Females predominate.

Ischiopagus Parasiticus.—Both sides of a double monster may be unequally developed, so that one portion appears as a parasite of the other. In ischiopagi, the head—or head and trunk—of one twin may be wanting. *Ischiopagus dipygus*, or double-buttocked, may be explained as follows (Fisher). We will imagine that the head and trunk and arms of one fetus are missing; then imagine that the two legs belonging to the parasite are drawn down until they are fused along their inner sides. Thus we have an individual with one normal trunk and upper extremities, two normal legs, and between them a compound leg, on either side of which is a set of external genitals. The dorsal aspect of the compound foot is turned forward, and the species is thus distinguished from the *Dipygi* proper, which will presently be considered. A unique case of this kind is that of Jean Baptiste dos Santos, born in Portugal in 1846, and perhaps still living. One picture shows him as an infant one year old, with a well-developed body and outside legs, and a compound leg between the others. The foot is double and the toes turn backward. On either side of the compound leg is a scrotum containing a testis; above the third limb are two smaller pouches, each of which contains a testis; these last went back into the abdomen later in life. Another picture represents him as a young man of twenty-two. He was able to hide his deformity under his clothes by strapping his extra limb to one of the others. He could use both penes in coitus, but preferred the left.

Pygopagus.—In this genus of the Katadidyma, the splitting from before backward has reached the maximum. The union is usually at the sacrum or coccyx, and might perhaps allow the name *Rhachipagus* to be given to the genus. The vital organs in the typical and symmetric form are distinct, although the rectum and the external genitals are sometimes more or less fused. In females the vaginae are usually separate, but there is a common vulva; in males there is usually one scrotum containing four testes, and the penis is single. The symmetric or autositic form is rare, both in man and animals; but parasitic varieties are common, especially among fowls. Since the vital organs are usually well formed and independent, the pygopagi are generally viable and may attain advanced life.

The most famous case of symmetric pygopagus is that of the Hungarian sisters, Helen and Judith, born in 1701. Helen first presented by the vertex and was delivered as far as the navel. After a delay of three hours the rest of the body passed, and then the body and head of Judith in reverse order. Some such mechanism as this is the common method in the birth of most double monsters. Menstruation came in each at different periods; they urinated separately from different urethrae; but, having a common rectum, they both felt at the same time the desire to defecate; the vulva and beginning of vagina were common, but the genitals above that point were distinct. They died at the age of twenty-one, from Judith's disease of the brain and lungs. The vertebral columns were fused from the second sacral vertebra to the tip of the coccyx.

The North Carolina twins, Milly and Christine, born in 1850 and still

alive as far as known, were similar in most respects to the Hungarian sisters.

Some of the forms of parasitic pygopus depart so far from the typical that their place in classification is dubious, some being little different from the sacral inclusions. A rather common form is that of the so-called Italian three-legged boy. He has an extra leg which seems to be attached to the sacrum of the normal body, making him a *Pygopus tripus*. Extra limbs attached to the rump are relatively common in animals, and especially so in fowls.

Anadidyma.—The *Terata anadidyma* are characterized by duplicity extending from the caudal toward the cephalic end. This duplicity is of all degrees, from mere splitting of the tip of the tail to the craniopagi, in which the junction is only by the tops of the heads. The division of this order into genera depends upon whether or not the duplicity involves less than all



FIG. 145.—Dipygus (pig).

the vertebræ or extends to include the cervical region or to involve the head.

Dipygus.—After the double-tails come the dipygi, in whom there is more or less of a double condition of the pelvis. According to the extent of the doubling, there will be room for a number of legs; and thus the species are distinguished, as *Dipygus dipus*, *tripus*, and *tetrapus*. In the more exaggerated cases there are two complete pelves bearing two complete pairs of legs (Fig. 145). The slighter cases have but little tendency to duplicity of the pelvic bones, but have a double condition of the external genitals. Many of the diphallie individuals are double monsters. Dipygus is rare in man, but more common in lower animals. A famous case of *Dipygus tripus* is that of Blanche Dumas, born in 1860 and probably still living. The belly and pelvis are broader than usual; between the normal legs is a third, on either side of which is a set of external genitals. The only external points of difference between her and dos Santos, as an *Ischiopagus dipygus*, is that

the third leg is single and that its anterior aspect points forward like the normal legs.

A probably unique case of *Dipygus tetrapus* is that of Mrs. B., reported by Wells. The pelvic region was very broad, and between the two normal legs were two smaller legs placed symmetrically, with the external surfaces toward each other and the inner surfaces toward the normal limbs. There seemed to be two complete sets of genitals, both external and internal. There were also two anuses. She became pregnant in the left uterus, but labor was induced for incoercible vomiting.

Syncephalus (Fig. 146).—By some authors these are classed with the



FIG. 146.—Syncephalus.

thoracopagi having two heads and called *Thoracopagus syncephalus*. In this genus the splitting has extended up to the head and often involves it, allowing the existence of two complete spinal columns and two sets of ribs. The duplicity often extends so far forward in the cranium that there are rudiments of a posterior face or at least an ear. The thoraces are united by the ventral aspects, as in the four-armed dicephali. A complete sternum is developed on each side of the common thorax, half belonging to each twin. The chest-cavities are common or divided by a membranous partition; there is a compound heart or two hearts; the gut is usually double below the duodenum; the diaphragm is double. The brain is double posteriorly; there are two cerebelli, two pontes, two medullæ, and sometimes a double condition.

farther forward. As in diprosopus, the duplicity and consequent mixing of the cerebral tissues probably account for the fact that these monsters rarely live long, even if born alive. On the contrary, the dipygi, having a single brain, though a more or less double body, are likely to live to adult age. The syncephalus is not a rare monster, and, like the other anadidyma, is especially common among lower animals.

Parasitism among the anadidyma is much rarer than among the kata-didyma; but among the dipygi and syncephali there are various examples of parasitic forms, in which one of the fetuses is more or less rudimentary.

Cephalopagus.—In this genus the bodies are entirely distinct and there are two heads, which may be joined at any point along the median line, from the occiput to the face. The point of union determines the species: thus, if joined at the cranium, the species is called *Cephalopagus craniodidymus*; if at the face, *prosopodidymus*. The two heads are not always arranged with perfect regularity in respect to each other, since the faces may look in different directions. The genus, especially the symmetric form, is the rarest form of monster except *Acardiacus acornus*. Most of the genus is of the parasitic form, in which there is an extra head with only a rudimentary body or none (Fig. 147). Because of the independence of the organs, this monstrosity is not incompatible with continued existence. The most famous case was observed in Bengal in 1783, in the person of a child, having joined to the vertex of its head another perfect head without trace of body. During life, although no sign of intelligence came from the parasitic head, yet its eyes always filled with tears when the autosite cried, and pinching the skin of the extra head caused its face to assume an expression of pain. The child died at the age of five years, from the bite of a cobra. The brains were distinct and separated by dura. Only two human examples are recorded of cranial attachment at the frontal region, one of which lived ten years and the other eight months. One of the former twins died and was cut away from its fellow; but the latter soon died, perhaps from sepsis. The human examples of *prosopodidymus* are all parasitic, and in most the parasite is very rudimentary. In one case the parasitic fetal parts were successfully removed by Prof. Pancoast.



FIG. 147.—*Cephalopagus iniodidymus parasiticus* (Dr. T. R. Williams, of Punxsutawney, Pa.).

Anakatadidyma.—In the anakatadidyma there is duplicity at both cephalic and caudal ends of the embryo, with union somewhere between, always involving the xiphoid region. The order is classified according to the extent of the duplicity, and therefore according to the amount of separation of the two halves. Following the general rule that, the more separate the brains and other vital organs in double monsters, the more likely are they to maintain a continued existence, we find that those forms like the

Siamese twins, in which the union is only by a comparatively small band of tissue and in which the spinal axes are rather far apart, are most likely to live after birth. The genera of anakatadidyma are *Prosopothoracopagus*, *Thoracopagus*, and *Omphalopagus*.

Prosopothoracopagus.—In this genus the union is extensive and the separation small. The two vertebral columns, as in all of this order, are completely distinct, but lie so close together that the two halves of the compound individual are intimately united. Although this form resembles the syncephalus, yet in the former there is a distinct split of the extreme cephalic end of the embryo. The rudiments of the faces are on the same side. The esophagus, stomach, and duodenum are common, the air-passages duplex; there is a single heart, showing traces of duplicity. The genus is very rare.

Thoracopagus.—This genus is characterized by junction of the two portions at the thorax. As in the syncephali, the sternums are split and each half is united to the opposite half of that of the other twin. The chest-cavities are united, and are separated from the abdomen by a duplex diaphragm; there are two hearts or a duplex heart in one pericardium; there are four lungs; the gut is single from stomach to ileum. The genus is the most common of the equally developed double monsters. Rarer species are the *Thoracopagus tribrachius* and the *Thoracopagus tripus*, distinguished as indicated by the names. On account of the complexity of the lungs, livers, and hearts of thoracopagi, it is rare for them to live very long.

Thoracopagus parasiticus is very rare. A famous example is that of Johannes Baptista Colloredo, born in Genoa in 1617. His picture shows a smaller body attached to the front of his chest and hanging from him. This parasitic portion was ill developed, having only one leg and clubbed hands with only three fingers on each. The parasite took no nourishment and seemed to lead a purely vegetative existence.

In thoracopagi, as in most double monsters, there is usually or perhaps always a *situs inversus* of most of the viscera of the right twin. Normally the embryo turns over on its left side very early in development, so that the dorsum lies toward the left of the ovum. In the cases of double embryos, if the twins lie far enough apart to enable both to take the left-sided position, there will be no transposition of the viscera of the right twin. This condition obtains in the case of many homologous twins. When the two are united so that the right twin must lie with its back to the right, there will occur a transposition of the viscera in the right twin.

Omphalopagus.—The line dividing thoracopagi from omphalopagi is not definite. In the latter there is at least a connection between the tips of the xiphoids, and therefore a cartilaginous portion to the uniting band. This band usually contains peritoneum and a portion of liver. Sometimes there is a double insertion of the navel-string by a forking at the fetal end, but often there is only one cord inserted at the middle of the bridge. The so-called Siamese twins, born near Bangkok, Siam, of Chinese and Cambodian parentage, are perhaps the most celebrated of all double monsters. They lived to be sixty-five years old, married, had each a large number of normal children, and lived a very interesting history. In infancy they were joined by a band of flesh and cartilage extending from the xiphoid to the navel, so that their ventral surfaces were in apposition; but, as they grew and stretched upon this band, it elongated enough to enable them to stand,

sit, and lie, side by side. The question of separation by a surgical operation was several times considered, but almost all surgeons advised against interference. Perhaps now, with aseptic technic, such an operation might be successful; but the existence of a large band of liver in the junction would at least cause severe hemorrhage. Each twin had a normal set of organs, but there was a *situs inversus viscerum* in Eng, the right twin. The hypogastric arteries ran to both twins from the umbilical cord, which was inserted in the lower part of the middle of the bridge. Two or three other cases of omphalopagus are recorded, in one of which the band was successfully divided by a gradually constricting ligature.

Omphalopagus parasiticus is not so rare as the parasitic form of thoracopagus. The Hindoo lad Laloo is an example. He has a headless parasite attached to his umbilical and xiphoid regions. This parasite has two arms and two legs, with a rudimentary body between; no head. The parasite is purely vegetative, has no anus, but passes urine involuntarily.

Triple Monsters.—Homologous Triplets.—Uniovular triplets, like homologous twins, are always of the same sex and are very similar in appearance and nature. An acardiacus may exist in the same chorion with two normal fetuses, or two acardiaca with a single normal fetus. One or two cases have been noted of a double monster in the same chorion with a triplet. If the different forms ever occurred, it would be possible to classify triple monsters according to the extent and direction of the triplicity, as in double cases; but only one case is authentically recorded of a triple monster.

Tricephalus Dibrachius Diauchenos.—The obstetrician, confronted by a second head, and thinking that he had a case of locked twins to deal with, amputated the first, only to be confronted by a third. The first two heads were amputated and the third perforated before the child could be born. The placenta was single, but of twice normal size; there were two vertebral columns and three necks, two chest-cavities, two sacra, two ischia, four ilia, and two pubes. The pelvic contents were normal; the genitals were male and single.

Single Monsters.—Single monsters and malformations do not lend themselves so readily to classification as those of a compound character. In the latter there is probably one cause, varying in degree or place of action merely, while single abnormalities may be caused by many different factors, some of which are yet unknown. During the early weeks and days of embryonic life, the anlagen of the different parts and organs are being laid down rapidly and assuming their adult form. During the later months, these anlagen do little more than grow. Arrested development, as Ahlfeld says, is not a force, but a condition, and cannot of itself account for the production of anomalies. Some force, internal or external to the embryo, must be the cause of arresting the development at different stages. This cause cannot in all cases be determined, but must always exist, and in most cases can be recognized. The extent and anatomic situation of the malformation will depend upon the time of the interference, the extent of the interfering force, and the part of the embryo upon which the interfering force acts. The variations of these three factors will produce wide variations in the effects produced. Time is perhaps the most important element. The force is mostly the same, although varying in amount; but, even to the extent of a few hours, the time at which that force acts is a factor of the utmost moment in determining how great and of what kind the malformation shall be.

The persistence of embryonic clefts is a considerable etiologic factor in the production of malformations. The ventral and neural cavities of the body are formed by the union of ventral and dorsal clefts, the different parts of which normally close at different embryonic periods. The nonclosure of the different parts gives rise to different anomalies, varying widely in appearance. Important causes for hindering the closure of these embryonic clefts are: increased accumulation of fluid within internal organs, increased size of internal organs, prolapse of parts between the still divided margins of the clefts, the presence of amniotic folds between the edges, disturbance of the spheric curving of the edges so that they do not meet throughout, and lack of enough material to close the cleft. Behind all these causes is probably disease of the chorion, amnion, or uterus, or perhaps infectious disease of the embryo itself. Adhesions of the membranes to the embryo may in various ways interfere with the development of a part or obstruct its circulation, so that injury is done to some of the embryonic cells. The disease of the membrane may soon recover, because we know that the regenerative power of embryonic tissues is great; or the adherent band may atrophy and disappear, so that at birth no trace may be found of what was at the time a powerful cause of evil. The loss of a few cells in the early stages of the development of a part, or the delay of some phase of development even for a few hours, may have, in the later history of the intra-uterine life of the individual, results far-reaching and immensely important.

Amniotic bands and adhesions may compress limbs so as to deform or even amputate them, may bind fingers and toes together so as to make them webbed, may hold limbs in constrained positions so as to make them clubbed, may close normal openings like the anus, or in countless ways may give rise to deformities. Defective development from causes more or less obscure may result in general dwarfism, in cyclops, in symphus, and in ectromelus. Just as in twin embryos the cause may be an excess of embryonic material, so in giants and in local hypertrophies excessive development in single individuals may be due to superabundance of formative material not sufficient to give rise to splitting of the undifferentiated embryonic cell-mass.

Gastroschisis.—Nonclosure of the ventral commissure occurs in man, and perhaps in animals, more often than nonclosure of the dorsal commissure. Defects are seen at all points in the face, chest, and abdomen.

Prosoposchisis.—At the fourth week, in the middle of the face there is a large hole, bounded below by the primitive lower jaw, on the sides by the lower jaw and the ununited rudiments of the upper jaw, above by a continuation of the frontal with its two nasal processes. This mouth-hole connects above with the nasal and optic cavities. This last communicating cleft lies between the outer nasal process and the upper maxillary process of the first gill-arch. All the abnormal clefts of the face are explained by nonclosure of one or more of these primary clefts at the proper time. The defect may be superficial or may involve the maxillary and nasal bones and even the palatals. In some cases the amniotic bands which caused the clefts have been seen after birth. In many it is probable that the band had atrophied and disappeared in part at an early period, so that the cleft had a chance to close partly. A line like a scar is often seen continuing the direction of a cleft. Double-sided fissure of the face is more common than single; sometimes, from lack of frontal bones, a facial fissure will extend up into the skull.

Fissure or defect in development of the lower jaw is much less common than the above; and when it exists there is usually, in addition, a considerable defect in the mouth and the neighboring structures. The ears are set closer together and toward the under part of the head, when the lower jaw is considerably defective or absent (Fig. 148). Agnathus or lack of lower jaw is rare in man, but common in lambs. Abnormal openings from the outside into the trachea or esophagus or between these tubes are very uncommon.

Nonclosure of the clefts between the gill-arches may result in branchial clefts, branchial fistulæ, or branchial cysts, according to the extent and position of the imperfect closure. The persistent cleft is more often the second or third, and the outer opening is commonly a few centimeters above the sternum and at the inner border of the sternomastoid.

Thoracocœloschisis. — Fissure of the thorax alone is rare in man, but more often exists in connection with fissure of the abdomen. Like the latter, it may be caused by a fold of the yolk-sac getting between the edges of the developing thoracic wall, hypertrophy or displacement of some internal organ, or other interference with closure of the two sides of the sternum.

Up to the end of the second week, the heart projects above the ventral plates which, by their union, are to form the anterior body-wall; therefore any hindrance to the closure of these plates in the median line is likely to allow the heart to be displaced forward, so that finally it lies wholly or in part outside of the chest-cavity. The region of the navel, normally the last to close, is a favorite seat of fissure. Persistent cysts of the urachus, hypertrophy of abdominal viscera, or other accident which places a body between the uniting halves of the abdominal wall, may cause the defect in the median line. Marked retroflexion of the embryonic body may force the abdominal organs between the edges of the ventral cleft, thus inhibiting its closure.

Fissure of the lower abdomen and fissure of the pubes are probably often or always caused by bursting of the allantois, which acts as the primitive bladder. Some cause which closes the normal opening of the allantois at the umbilical end of the urachus, after the primitive closing of the opening into the cloaca at the second week, would compel the urine to distend the allantoic sac enough to burst it. Then the fluid would pass directly into the amniotic cavity through the rent, and thus prevent union of the bladder and pubic articulation in front. This fissure of the bladder may extend to the urethra or involve only that canal, as in the condition known as epispadias. This defect in the dorsum of the penis is a rare condition, occurring only once to 150 cases of hypospadias, or defect of the lower side of the penis and urethra. Up to about the fifth week, the gut and urinary passages open into the allantois and find outlet by way of the urachus and umbilicus.



FIG. 148.—Agnathus ectromelus apus.

If the re-opening of the cloaca is tardy, the allantois fills and distends as the urachal opening closes; and this distention of the allantois may prevent union of Mueller's ducts, and thus cause double uterus or vagina.

Hermaphroditism.—Until the etiology of sex is determined, it will be impossible to make a clear and full explanation of the phenomena of hermaphroditism, which cannot be said to consist merely in anomalies in closure of the urogenital cleft. In the early embryo, sex is apparently neuter. Locally, hermaphroditism consists in persistence in one sex of some of the structures belonging to the other sex, but which are normally present in an early period of the embryonic existence. The external genitals are formed by union in different ways of the margins of the urogenital cleft and cloaca. In the male the union is complete, while in the female there is left a cleft which becomes the vulva and opens into the vagina. Internally the genital organs are formed in the male from the Wolffian body and duct, and in the female from the Muellerian duct. In either sex normally the unused duct atrophies, but in internal hermaphroditism more or less development of the other ducts takes place. Where there is an anomalous development of the external genitals, there is apt to be also an anomalous development of the internal genitals. Besides these factors, there are usually general bodily and mental characteristics of the simulated sex present in the individual. True hermaphroditism, involving the production in the same person of both ova and spermatozoa, has never yet been authentically recorded, although there have been instances of the presence of organs histologically like ovaries and testes.

Klebs classifies true hermaphrodites (so called) and pseudohermaphrodites.

True Hermaphroditism.—These cases have both ovaries and testes, and take their gender from the organs which functionate. They may be *bilateral*, with an ovary and a testis on each side; *unilateral*, with an ovary on one side and a testis on the other; *lateral*, with both an ovary and a testis on one side and no sexual gland at all on the other. In all these cases, there will also be an amphimorphous condition of the external genitals. Very few cases are authentic.

Pseudohermaphroditism.—In these cases the sexual glands will be either ovaries or testes, but there will be an amphimorphous condition of the external and internal genitals. There are male or female pseudohermaphrodites, according to the sex of the glands. Autopsy is sometimes necessary to verify the sex, which, in the large majority of instances, is masculine. The degrees of male pseudohermaphroditism run from the mere enlargement of the prostatic vesicle, through the cases of rudimentary penis with more or less hypospadias, to those with a complete uterus masculinus, tubes, vagina, and urogenital cleft. Female pseudohermaphroditism is very rare and requires very strong evidence to be credited. Such individuals have a rudimentary vagina, and sometimes a uterus, a hypertrophied clitoris which more or less resembles a hypospadiac penis. The ovaries are sometimes prolapsed into the labia, making the last look like a scrotum.

In cases of even slight pseudohermaphroditism, where the generative organs only slightly resemble those of the opposite sex, there are usually appearances of the other sex in other parts of the body or even in the mental and moral nature. Thus a man with marked hypospadias, rudiments of a vulva, and a small penis is very apt to have something of the female type to his shoulders, breasts, or hips, to have scanty beard or the female type of pubic hair.

Craniorhachischisis.—The neural canal runs the whole length of the dorsum of the embryo, and closes at different times in different parts of its course by a folding-over of the posterior vertebral and cranial plates. Incompleteness of this normal closure in any or all parts results in the deformity in question. Dropsy of the cerebrospinal tissues, membranes, or central canal may be one cause of such nonclosure. Such a dropsical condition is a very common disease of the fetus, and is due to disturbances in circulation, perhaps resulting from cardiac or renal disease in the embryo, and often associated with edema of the whole body. Such cerebrospinal dropsy may cause hydrocephalus with stretching of the cranium, atrophy of the contained brain or more or less defectiveness of the bony covering, with consequent deformity of the brain, depending upon the time when the hydrostatic pressure is first exercised.

Hydrocephalus of the congenital kind is almost always internal, involving the ventricles. The internal pressure may cause atrophy of the cerebral tissue and enlargement and thinning of the cranial bones, with increased number and size of the fontanel. On account of hindrance to development of the forebrain, from which the primitive optic processes start, hydrocephalus is often associated with defective development of the eyes. When there is a pressure from a collection of fluid in the ventricles, and the bony vault is partly lacking, there results a protrusion of part of the cranial contents which is known as encephalocele, hydrancephalocele, meningocele, or hernia cerebri. In these cases, the cranial contents are partly included within a fluctuating tumor having its base in the cranium. The great majority of such protrusions are in the occipital region. If the destructive effect of the intracranial pressure is sufficient and acts at the proper time, there may be complete absence of the bony covering of the brain and cord, with more or less complete loss of these structures.

By no means all the forms of craniorhachischisis can be explained by pressure of dropsical fluid within the craniovertebral cavity. Those forms particularly in which there is a greater or less retroflexion of the fetal body, and also those in which a considerable mass of brain-tissue lies uncovered by bone, can hardly be explained in this way. For the exencephali at least, and probably also for a large number of the anencephali, the cause is doubtless an adhesion of some part of the amnion to some part of the dorsum of the embryo, and a consequent distortion of the coverings of the brain and cord. Circulatory disturbances, or even infectious amniotitis, not infrequently exist, especially at early embryonic periods. These disorders may easily cause adhesions of the overlying amnion to some part of the ectodermal layer of the embryo. A common place for such adhesions would naturally be where the amnion lies close to the embryo, such as the dorsum of the head and cervical region, where the cephalic end of the embryo dips down into the ovum. This is also the earliest portion of the amnion to form, and this portion of the embryo is the most often affected with defective closure of the neural canal. The adhesion for a time of a part of the amnion would destroy certain cells, while the neighboring cells would go on in their work of developing the surrounding parts, so that a defect would result which might cause grave malformation of the dorsum of the fetus and retroflexion of the fetal body. The rest of the body would grow, while the cells affected by the adherent amnion would for a time remain stationary; and at the same time, enough cells of the embryo would be destroyed to

cause a defect in the covering of the brain and cord or of these structures themselves. Traces of such adherent bands are sometimes found at birth (Fig. 149).

Craniorhachischisis may be divided into three genera: *Anencephalia*, in which there is more or less complete absence of brain; *Exencephalia*, in



FIG. 149.—Anencephalus showing persistent adherent amniotic band.

which there is considerable brain-tissue placed wholly or partly outside of the cranial cavity; and *Spina bifida*, in which the chief defect is in the dorsal plates of the vertebræ. With the first two, the third often co-exists.

Anencephalia.—Two species may be distinguished: the first with retroflexion of the fetal body (Fig. 150), which is usually accompanied with

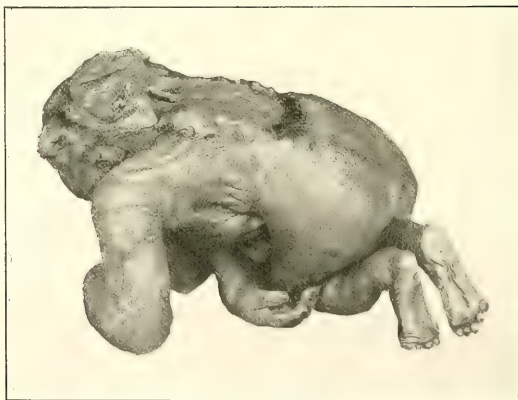


FIG. 150.—Anencephalus.

more or less *spina bifida*; and the second without retroflexion, where the vertebral canal is usually open only in the upper cervical region. *Anencephalus*, which is the most frequent form of monstrosity, is characterized by absence or the merest traces of brain and by extensive defect in the bony

vault of the cranium. The squamous portions of the cranial bones are so rudimentary that the head looks as if removed just above the forehead and ears. The base of the skull, deprived of the pressure of the brain above it, usually becomes concave and therefore foreshortened. These monsters seldom live more than a few minutes and never more than a few days, probably because they lack the influence of a brain to direct the vital processes. On the other hand, the bodies are often remarkably well developed and nourished, sometimes enough to cause dystocia on account of the size. The cranial and spinal nerves are present. Other malformations, especially those which seem to be due to the influence of amniotic bands and adhesions, such as harelip, club-foot, amputated limbs, and the



FIG. 151.—Hyperencephalus.

like, frequently co-exist. The sex is female in more than three-fourths of the cases. In the retroflexed species, on account of the lordosis and tilting-back of the head, the neck-furrow is obliterated and the head seems to be set low between the shoulders. The lordosis is greatest in the cervical region, so that here is left a deep cavity in the vertebral canal. Those cases which have rudiments of brain-tissue upon the base of the skull are called *pseudencephali*. The base of the skull and vertebral canal (if open) are covered with membrane, around which is a fringe of hair in a horseshoe form. Since the supra-orbital ridges are the topmost parts of the skull, they make the eyes stick out and give the frog or owl appearance so often described.

Exencephalia.—In this genus there is a defect in the cranium, through which the brain or its membranes protrude, lying outside the cranial cavity to a greater or less degree. The genus is divided into species, according to the place of exit of the encephalocele.

Proencephalus has a defect in the anterior part of the skull, the orbit, ethmoid, frontonasal region, or frontal bone. The hernial protrusion is usually largely meningeal, containing little cerebral tissue. The tumor may present in the orbit, in the nasal cavity, in the pharynx, alongside the nose, or in the forehead. The form is rare.

Hyperencephalus (Fig. 151) is that species in which the bony defect is in the vertex, usually involving the frontals and parietals. It varies in extent from a small meningeal tumor at the top of the head to one which contains



FIG. 152.—Notencephalus.

almost the whole brain, in consequence of which the cranial bones are rudimentary. Podencephalus is the term used to designate these extensive forms.

Notencephalus is characterized by a defect in the occiput (Fig. 152), through which the cerebral tumor protrudes, to hang down the back of the neck like a chignon. Depending chiefly on the size of the opening in the bone, the tumor may be large or small, containing little or most of the brain. In the latter case, the rest of the cranial bones will lie flat against the base and be rudimentary, because not stretched out by the growth of a normal brain within them. If the tumor is small and can be protected from external injury, the child may live indefinitely, even to adult life.

Iniiencephalus is characterized by a defect in the middle of the squamous portion of the occiput, accompanied by a fetal retroflexion and cervical spina

bifida so situated that the brain lies upon the bodies of the cervical vertebræ, but is covered by the bones of the cranial vault. The margins of the occipital defect articulate more or less completely with the margins of the spina bifida, thus closing in the brain. If this articulation is complete, there will be no protrusion of the brain-tissue at all; otherwise there may be an encephalocele in addition. Iniencephalus is relatively rare; less than thirty cases have been reported.

Exencephalus proprius (Fig. 153) has the fetal retroflexion, cervical spina bifida, and tilting backward of the head, as in iniencephalus; but the bones of the cranium are rudimentary, so that the brain lies exposed upon the base of the skull or the vertebræ. Males predominate, and the species is rare.

Spina Bifida.—This malformation is very common, existing both in connection with cranioschisis and alone. The vertebral laminæ do not unite for



FIG. 153.—*Exencephalus proprius*.

part or all the course of the column, and the transverse processes lie flattened out. There may be a membrane covering the open spinal canal, under which are spread out the flattened fibers of the cord; or, if the opening is circumscribed, the meninges may protrude between the divided bones in the form of a sac, sometimes covered with skin and sometimes with a membrane derived from the outer side of the dura. The inner lining of the sac is the inner surface of the spinal membranes, the contents are cerebrospinal fluid, and nervous filaments run along the walls of the cyst. The most common seats of spina bifida are the lumbar and cervical regions, parts of the canal which normally close last.

Cyclopia.—Cyclopia or synopsis is an example of defective development of the anterior parts of the brain and of the optic buds. In microcephalus, there is a defective development of the whole brain. The eyes develop from budding forward of projections of the forebrain. When from causes more

or less obscure the forebrain is defectively developed, the eye-stalks may start close together or even be fused; so that when the optic vesicle reaches its full length, only one eye or a fused eye will be formed. The optic vesicles are begun very early, before the bones or before the union of the parts making up the face; so that, if the cyclopic eye already occupies the center of the face, the nasal plates are forced to grow elsewhere, usually above the eye. For this reason, we commonly have a rudimentary and often grotesque proboscis jutting out from the middle of the forehead above the eye. The internal bones and cavities of the nasal apparatus are lacking. Cyclopia runs through all degrees, from mere narrowing of the space between the eyes to a single optic globe or orbit or even total absence of the eye. The brain is always more or less defective in the anterior portions. The monsters are not viable.

There are certain irregular actions of amniotic bands and adhesions which produce various forms of malformation. In the so-called amputations of limbs, it is doubtful if the umbilical cord or amniotic band actually cuts off limbs already formed; but it seems more than likely that pressure of such bands, and also adhesions of parts of the amnion with the ends of limb-buds, may prevent further growth, so that such a limb or digit in later life appears as if cut off. Bands may bind digits together so that they appear webbed, or even, at an early stage, extensive contraction or adhesions of the amnion may cause the anlagen of both legs to fuse and produce *Sirenomelus* or sympodiatic monsters. The different forms of *Ectromelus* may have a similar etiology.

The conditions of talipes, atresia, local and general hypertrophy, local and general dwarfism, and various other malformations, as well as the hemiterata and heterotaxis, are considered in other parts of this work.

SPECIAL PATHOLOGY.

THE BLOOD AND THE BLOOD-MAKING ORGANS.

METHODS OF BLOOD-EXAMINATION.

It seems best to give a brief account of the principal methods and instruments by which our present knowledge of diseased states of the blood

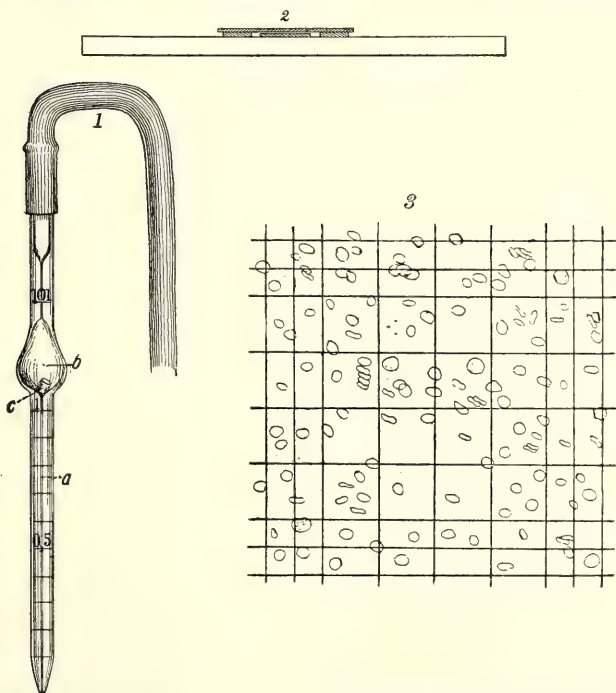


FIG. 154.—Thoma-Zeiss blood-counting apparatus. 1. Mixing apparatus: *a*, Capillary tube in which the blood is taken; *b*, chamber for mixing the blood with the diluting solution; *c*, glass ball to aid in mixing the blood with the diluting solution. 2. Cross-section of the chamber in which the blood is counted. 3. Section of the field on which the blood is counted, showing thirty-six squares.

and blood-making organs has been built up. These are : Examination of the fresh blood (uncoagulated) ; enumeration of the red corpuscles and of the leukocytes ; hemoglobin-estimation ; examination of stained cover-glass

preparations of the blood, lymph, and fresh bone-marrow; bacteriologic examination of cultures from the blood; examination of the serum (serum diagnosis).

Other methods of examination, such as those dealing with the alkalinity, isotonic coefficient, rapidity of coagulation, freezing-point, molecular concentration, hemolytic and bacteriolytic properties, and chemical composition of the blood, do not fall within the scope of this article.

Examination of fresh blood, which is especially valuable in the search for parasites, such as the malarial organism, the spirochete of relapsing fever, and the *Filaria sanguinis hominis*, is performed as follows:

Carefully clean and warm a slide and cover-glass; puncture the lobe of the patient's ear with a bayonet-pointed surgical needle; touch the *summit* of the exuding blood-drop with the center of the cover-glass (held with pincers) and immediately drop it upon the warmed slide. The blood should spread so evenly that rouleaux are not formed and the red cells do not overlies one another. If it is desired to keep the specimen fresh for more than twenty minutes, the margins of the cover-glass may be sealed to the slide with vaselin or cedar oil.

Counting Blood-corpuscles.—The instrument of Thoma-Zeiss (Fig. 154) is the best. It consists of a pipet (*a*), in the bulb of which (*b*) a given amount of the blood is mixed with a neutral diluting solution 100 or 200 times its bulk,¹ by sucking blood up to the mark "0.5" on the tube and then sucking the diluting solution after it until the bulb (*b*) is full of the mixture. A drop of this mixture is then blown out upon the disk (Fig. 154), the size of the drop being calculated so that, when the "roof" of the counting-chamber is let down over it, the drop covers the disk without spilling over into the "mote." On the surface of the disk, which is ruled in squares of $\frac{1}{400}$ of a square millimeter, the corpuscles settle evenly and can be counted. At least 200 small squares should be counted. The average number of corpuscles in 1 square multiplied by 800,000 gives the number in 1 c.mm. of blood, if the dilution be 1:200.

For counting red corpuscles a convenient diluting solution is that of Gowers, made as follows:

Sodium sulphate,	gr. iiij;
Dilute acetic acid,	3j;
Water,	3iv.

Or Torson's fluid, which also stains the white corpuscles. This consists of

Methyl violet,	0.025 gm.;
Glycerin,	30 c.c.;
Distilled water,	80 c.c.

To this is added

Sodium chlorid,	1 gm.;
Sodium sulphate,	8 gm.;
Distilled water,	80 c.c.

The solution is then filtered.

The white corpuscles appear on the ruled surface of the disk (*a*), when Gowers's fluid is used, not much whiter than the red ones, but much

¹ Ten or twenty times its bulk when the leukocytes only are to be counted.

more highly refractile. The number present in a dilution of 1:200 is so small that considerable errors result from calculations based on it. It is better to dilute only 1:20 when we desire to count the leukocytes, using a large-bore pipet made by Zeiss for the purpose and a $\frac{1}{3}$ per cent. aqueous solution of glacial acetic acid. This renders the red cells invisible and leaves only the leukocytes in the field. The whole number present on the ruled surface should be counted in each of at least two drops. The total number found in two drops multiplied by 100 gives the number per c.mm. of blood.

In practised hands the error is not over 5 per cent. There are many important details in the correct technic of blood-counting, for which we

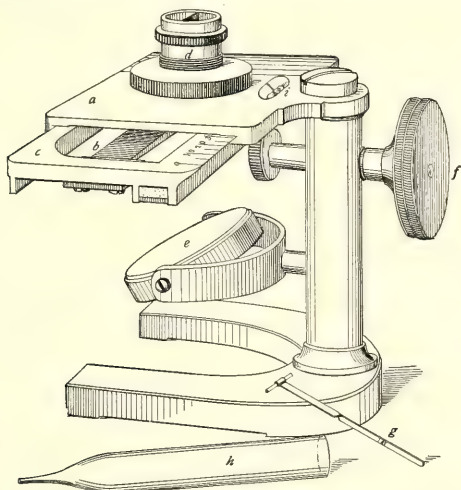


FIG. 155.—Von Fleischl's hemoglobinometer: *a*, stand; *b*, narrow wedge-shaped piece of colored glass fitted into a frame (*c*), which passes under the chamber; *d*, hollow metal cylinder, divided into two compartments, which holds the blood and water; *e*, white plate from which the light is reflected through the chamber; *f*, screw by which the frame containing the colored glass is moved; *g*, capillary tube to collect the blood; *h*, pipet for adding the water; *i*, opening through which may be seen the scale indicating percentage of hemoglobin.

have here no space; they may be studied in special treatises on the subject.

Hemoglobin Estimation.—Von Fleischl's hemoglobinometer (Fig. 155), which is in general use, has a very wide range of error. The principle of the instrument is the endeavor directly to compare the tint of a measured amount of blood with the tint of various portions of a wedge of red glass, the color of which shades gradually from deep red at one end to clear glass at the other. In most hands an error of 10 to 20 per cent. is inevitable. Gowers's hemoglobinometer depends also on the principle of color comparison, but instead of a wedge a tube containing colored gelatin is used. The error is not so large as with Fleischl's instrument, but the color of the wedge fades a little in time, making the reading higher than it should be.

Examination of Stained Specimens.—A drop of blood taken on the surface of a clean cover-glass, as above directed, is covered with a second cover-glass in such a way that their corners do *not* coincide. If both are perfectly clean and are held with forceps, the blood instantly spreads so as to make a layer one cell thick. As soon as the blood stops spreading, the upper cover-glass is rapidly slid off without raising or tilting it, and an even layer is left on each glass.

After drying in the air, such specimens are best fixed by heating in an oven to 120°–140° C. or by passing them from fifteen to twenty times through the tip of a Bunsen-burner flame. If the latter method is used, we can only determine by practice how rapidly the cover-glass should move through the flame. Overheated specimens stain too faintly; underheated ones stain too intensely. The happy mean can be learned only by experience.

By far the best stain for such specimens is that known as Ehrlich's "triacid" mixture. The formula is as follows:

Sat. aq. sol. orange G., ¹	120–135 c.c. ;
Sat. aq. sol. acid fuchsin,	80–165 c.c. ;
Sat. aq. sol. methyl green,	125 c.c. ;
Glycerin,	100 c.c. ;
Absolute alcohol,	200 c.c. ;
Water,	300 c.c.

A single drop of this mixture is spread with a glass rod on the specimen and left there at least three minutes, or as much longer as is convenient. It is impossible to overstain a properly prepared and fixed specimen. The stain is then washed off with water, the specimen dried with blotting-paper and mounted in balsam. Hewes has improved upon this stain by counterstaining the covers for one to three seconds with Löffler's blue. The nuclei are much better seen in this way. The appearances of a specimen so prepared will be described later.

Examination of the fresh marrow is best made by smearing as thin a layer as possible between two cover-glasses, which are then fixed and stained as above directed.

Pieces should be hardened in Zenker's fluid and embedded and cut in the ordinary way. Eosin and hematoxylin form the best stain for such preparations.

Bacteriologic Examination.—Render the skin over the surface of the bend of the patient's arm reasonably aseptic. Compress the arm above the elbow so as to make the veins stand out. Plunge the needle of a sterile hypodermic syringe into the largest vein visible and withdraw a syringe-ful of blood. This blood can then be poured down over the slant of a blood-serum or agar-agar tube or mixed with softened agar-agar, according to the nature of the organism looked for. In cases of ulcerative endocarditis, pyemia, pneumonia, and gonorrhea, micro-organisms are not infrequently obtained in this way.

Serum Diagnosis.—(See pages 237 and 270.)

¹ Colors are best obtained of G. Grüber & Co., Leipzig.

DISEASES OF THE BLOOD AND THE BLOOD-MAKING ORGANS.

INTRODUCTION.

The limits of this subject are becoming constantly more difficult to define. Strictly speaking, there are no diseases which we know to affect primarily the blood, except possibly malaria and a few other parasitic diseases. All diseases probably affect the blood to a greater or less degree, and it is arbitrary how many we include under diseases of the blood itself.

There seems to be almost as much reason for classing diabetes and other so-called constitutional diseases with blood diseases as there is for including chlorosis. The blood changes are results of deeper causes equally in the one case as in the other. Every change which we describe in our accounts of diseased blood is a symptom which may result from any of various causes. In some cases, as in secondary anemia, we are aware of the fact that the blood changes are only symptomatic of some underlying malady, like cancer or cirrhosis of the liver. In chlorosis and pernicious anemia, there is but little likelihood that the blood changes are any less "secondary," since they are identical with conditions of the blood due to well-known causes, such as intestinal parasites or traumatic hemorrhage. In all probability the blood of pernicious anemia and chlorosis simply reflects the action of deeper and more primary causes, the nature of which is at present not understood. As we now speak of "diseases of the blood," so we should have to speak of "diseases of the urine," and probably to include therein the changes which the urine undergoes in a great variety of diseases, were it not that we have in this case definite organs—the kidney, the bladder, etc.—which we can examine in connection with urinary changes, and thus correlate certain of the urinary disorders with disease in one or another of these organs. As regards the blood, we are not so far advanced. The reproduction of blood-tissue probably occurs in a great many different places, no one of which is set aside for that function alone—like the heart for pumping, or the bladder for storage.

All diseases affecting the various localities in which blood-cells breed cannot be classed as diseases of the blood or blood-making organs. Thus, although we ordinarily speak of the bone-marrow and the lymphatic apparatus (adenoid tissue wherever found) as blood-making organs, we should not think of classing osteomyelitis or syphilitic adenitis under blood diseases.

If, on the other hand, we drop the "blood-making organs" altogether, and class under "diseases of the blood" all such and only such as show relatively striking changes in the circulating blood-tissue itself, we should be bound to exclude Hodgkin's disease and the hemorrhagic diseases (scurvy, purpura, hemophilia, etc.), in which no marked alterations of the blood are, as far as we know at present, constant; and furthermore, to include diabetes, Asiatic cholera, and the bubonic plague, in all of which the blood shows as great aberrations from normal as in chlorosis.

It is best, therefore, to admit that we have no good or sufficient reason either for our inclusions or for our exclusions, in making out our list of diseases of the blood. Under this heading are classed for convenience a number of quite heterogeneous pathologic conditions which do not easily find a better

place in other groups and which custom and outgrown theories have placed together. Having no better positive classification to propose, we shall in this article include the traditional list, viz.: Secondary anemia, chlorosis, pernicious anemia, leukocytosis, leukemia, Hodgkin's disease, hemophilia, scurvy, purpura.

In order to make intelligible what is to be said in the next section as to pathologic conditions of the blood, some general description of the normal morphology of the blood must be attempted. We usually speak of blood as made up of red corpuscles or erythrocytes, white corpuscles or leukocytes, blood-plates, and plasma, in which the above elements move or are carried.

Red Corpuscles.—In the circulating blood of healthy adults, the so-called red corpuscles are recognized easily as circular, slightly biconcave disks from 6μ to 9μ in diameter and about 1μ in thickness. In infancy, larger and smaller forms are found, even in health; but in the adult, anything beyond these limits is considered pathologic. Seen by transmitted light, the "red" corpuscle is of a very pale, slightly greenish-yellow color. No distinct nucleus is made out, although Arnold and others adduce evidence that in the mature cell there are appearances which might correspond to the *remains* of the nucleus which is present in every red corpuscle at an earlier stage of its development. In early embryonic life, all red blood-cells are nucleated and are mostly of much larger size than those seen in postembryonic life. Later in embryonic life, they begin to lose their nuclei, which break up and fade out; and such nucleated cells as are still seen are much smaller, in the main, than those of embryonic life. Finally, at birth and thereafter, there are no nucleated cells in the circulating blood; but in the bone-marrow the smaller nucleated forms persist, and are especially plentiful there after hemorrhage, in the course of acute infectious diseases, or in anemic conditions when blood repair is called for. The bearing of these facts on diseased conditions of the blood will be seen later.

Although it is generally agreed at present that red blood-corpuscles are developed from nucleated corpuscles or erythroblasts—which are formed in embryonic life in the liver, spleen, and elsewhere, and in adult life in the bone-marrow alone—their *primary* origin is still a matter of doubt. The weight of opinion seems to support the view that red cells are not developed from leukocytes nor from an ancestor common to both red and white corpuscles, but have an independent origin, probably from the angioblastic cells of the mesoblast.

In healthy adults the number of red corpuscles is about 5,500,000 per cubic millimeter. They stain well with acid anilin dyes (eosin, fuchsin, etc.), and comparatively feebly with basic dyes. In certain pathologic conditions, their affinities become neutralized or reversed.

Leukocytes.—Among other tissues of the body, "red" corpuscles can be distinguished by their hemoglobin, which gives them a peculiar color and staining reaction;¹ and even when they are nucleated they can be distinguished from other tissues in this way.

For leukocytes, on the other hand, we have no such distinguishing mark. We cannot simply agree to call all colorless cells found in circulating blood by the name of leukocytes and exclude all others; for, aside from the well-known fact of the "emigration" of leukocytes from the vessels and into

¹ It is true that we have no absolutely unique and specific staining reaction for hemoglobin, but there are very few conditions in which other cells stain like it.

various tissues, we find cells in all respects similar to leukocytes which reside permanently or almost permanently in various other places. It is generally agreed, for example, that the small mononuclear cells which are so plentiful in fluid lymph and chyle and in lymphatic glands are identical with the smallest forms of blood-leukocytes, and that the majority of the cells in ordinary pus are identical with the larger forms of blood-leukocytes. It is further shown by recent English researches that the large body-cavities contain large numbers of free cells, many of which are in all respects similar to the coarse granular leukocytes of circulating blood, and other cells which are occasionally seen in the blood. That the cells which make up the germ-centers of lymphoid tissue and the bulk of those found in normal bone-marrow (exclusive of fat) may also be found in the blood is likewise well established.

The wandering cells of the alimentary canal, of the diaphragm, and many of those found in connective tissue are in all probability to be classed as leukocytes more or less altered by the conditions of their environment.

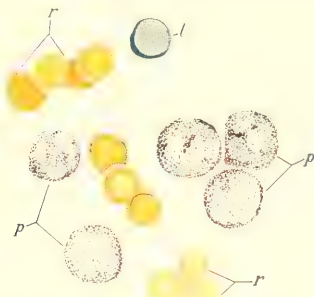


FIG. 156.—Leukocytosis: *l*, lymphocytes; *p*, *p*, polynuclear neutrophils; *r*, *r*, red cells. (Cover-glass film from a case of pneumonia, stained with Ehrlich's "triacid" and drawn with camera lucida.)

This includes the mast-cells of connective-tissue structures. As to Unna's "plasma-cells," I am not prepared to speak confidently; but they also are very possibly to be included under the same heading. Cells very closely resembling them may be seen in the blood of lymphatic leukemia. The varieties included in this list are not more different from each other than from the different types of colorless corpuscles always present in normal circulating blood. If it be objected that the term "leukocyte" is thus made a sort of "omnibus" into which is packed a heterogeneous mass of cells of all types, the answer is, first, that the leukocytes of circulating blood are equally heterogeneous; and secondly, that transitional forms between each of the varieties can be found.

The differences between them are probably due to (*a*) differences in the ages of the different cells, and (*b*) to differences in environment (marrow, celomic spaces, blood, connective tissue) into which they wander.

Representatives of all these types are found in the marrow, where no doubt many of them arise; and here, as in the spleen, body-cavities, and elsewhere, we find the giant cells or macrophages, which differ from the

leukocytes of circulating blood only in the size to which their free quarters allow them to develop. They are too large, many of them, to pass the capillaries.

Our knowledge of these various forms would never have been possible without the use of the combinations of anilin staining methods introduced by Ehrlich. With the aid of his staining methods we recognize in normal blood the following types of leukocytes:¹

Lymphocytes.—Spheric cells from 5 to 10 μ in diameter, mostly filled by a spheric nucleus,² nonameboid, indistinguishable from the small elements of lymphoid tissue and lymphoid infiltrations or from the lymph- and chyle-corpuscles. The nucleus stains intensely with simple basic stains. With Ehrlich's triacid mixture the nucleus is often pale and shows a delicate chromatin network. The protoplasm may not stain at all with acid dyes. It can be stained irregularly with basic dyes, the extreme periphery showing a greater affinity for basic dyes, while the portion in contact with the nucleus shows a preference for acid stains. With double or triple stains, it often shows its affinity for both kinds of dyes by taking up a mixture of two or more dyes. Thus, with eosin and methylene-blue, it may stain purple; with Ehrlich's triacid mixture, gray. Basic stains bring out coarse blue granules in the protoplasm of some of the lymphocytes.

Other cells are like those just described, but considerably larger and with a relatively larger amount of protoplasm. Such cells may be from 10 to 17 μ in diameter. In the large forms the nucleus stains less well and is not infrequently more or less indented or bent, with its borders ill-defined.

In the blood of many healthy persons there may be seen every intermediate size between this variety and that first described, so that the distinction appears entirely arbitrary. In other cases, all cells of this general type are either under 8 μ or over 13 μ diameter, with none at all of the sizes intermediate between these measurements. In such cases, either the small type or the large may be the more numerous. As a rule, the small forms are four or five times more numerous than the large. Together, the large and the small lymphocytes make up from 25 to 45 per cent. of the colorless corpuscles of normal blood. Their number is considerably increased after meals and by various other influences. The larger forms are somewhat ameboid and phagocytic. In the protoplasm of the larger forms, especially near the periphery, fine basophilic granules may be seen.

Polymorphonuclear Neutrophiles.—Diameter in cover-glass specimens ordinarily from 11 to 15 μ , averaging 13.5 μ ; nucleus sausage-shaped, occupying a relatively small space in the cell-body and taking on a great variety of contorted appearances, whence its name. In many instances the nucleus appears to have divided into two or more segments, but good staining usually shows that the apparent divisions are bridged by constricted portions which join the large nuclear fragments with one another. This nucleus stains more deeply and shows less structure than that of any other variety of leukocyte. The protoplasm stains diffusely with aqueous solutions of acid dyes; very faintly, if at all, with basic dyes. Alcoholic solutions of acid dyes (eosin, acid fuchsin) bring out a fine pinkish granulation in the protoplasm. These granules are much more distinctly brought out by differential acid stains,

¹ The confused nature of the terminology here followed is apparent to the writer. But, in the absence of a better basis of classification, the traditional one is adhered to.

² Rarely indented or divided.

such as Ehrlich's triacid. They have been called "neutrophilic" because neither simple acid stains, like eosin, nor simple basic stains, like methylene-blue, bring them out clearly. There are probably no genuinely *neutral* stains in use. With Ehrlich's triacid mixture, these granules stand out as purple or violet dots against a colorless or faintly pinkish background. They are seen over and around, but not *in*, the nucleus.

These cells are actively ameboid and phagocytic, although they do not have by any means a monopoly of the function of phagocytosis, which is also exercised by the large lymphocytes. At rest outside the body and in the bone-marrow, the nucleus assumes a spheric shape. Its twisted and irregular shape is probably due partly to its ameboid movement, partly to growing old.

Between this cell and the lymphocytes we see scarcely any transitional forms in normal circulating blood. But in some cases of leukemia many intermediate forms are seen, as also in smear preparations from the normal bone-marrow.

Polymorphonuclear neutrophiles make up from 60 to 70 per cent. of the leukocytes of normal circulating blood. In the celomic spaces they are much less numerous, while the lymphocytes and eosinophiles are much more plentiful there than in the blood. The great majority of cells in ordinary pus are neutrophiles. In the blood of lower animals there are no neutrophilic cells.

Eosinophiles.—From 1 to 4 per cent. of the white corpuscles of normal blood show, when stained with eosin, a number of brilliantly colored pink granules in their protoplasm. These granules are much larger and more highly refractive than the neutrophilic granules, and are nearly of uniform size. They are spheric or more rarely oval, and no cell-body can be made out between them by any method of staining. They are grouped loosely around or at the side of the nucleus, which seems attached to them rather than embedded in them. The nucleus stains feebly with basic dyes, and it is difficult to make out a structure in it. Frequently it is divided into two or more parts, between which no connection can be made out. The cell, as a whole, is slightly smaller than the neutrophile and much more irregularly shaped. It is the most actively ameboid leukocyte. In normal blood eosinophiles are few; but in the celomic spaces, in the bone-marrow, and in connective tissue, they are much more abundant. Transition forms between them and the neutrophiles do not occur in normal blood.

Mast-cells.—In normal blood these cells constitute about $\frac{1}{2}$ per cent. of the leukocytes. Their nucleus is irregularly trilobed and embedded in a protoplasm which with Ehrlich's triacid remains unstained, but with basic stains shows irregular clumps of dark blue. In myelogenous leukemia they are frequent.

This completes the list of varieties of leukocytes in the blood-vessels of normal adults. The absence or great rarity of transitional forms between any of the three varieties just described makes it very unlikely that such transitions take place in the peripheral circulation. On the other hand, the fact that in leukemic blood and in the normal marrow may be found an abundance of transition forms of all kinds makes it unlikely that the different varieties seen in normal circulating blood are ultimately of different origin. In the peripheral blood we get only a short phase of the development of leukocytes, viz., from the small to the large lymphocyte. Then there is a gap

between the large lymphocyte and the polymorphonuclear neutrophile, the intermediate forms being found chiefly in the marrow. Among such intermediate forms should be reckoned the *myelocyte*, to which reference will be made later. Possibly also the various types of *basophiles* (*vide infra*) are to be looked upon as normal phases of development of leukocytes in certain environments, under conditions furnished by the marrow, the celomic and connective-tissue spaces, but not by the blood. We need not assume that every leukocyte normally goes through all these stages. They may all start alike—*i. e.*, as lymphocytes—but be so affected by the conditions of their environment that some never get beyond the lymphocyte stage, while others develop into neutrophiles, basophiles, or eosinophiles, according to their surroundings. The blood receives from various sources a given number of cells in various stages of evolution. What are the laws which govern the number of each variety that shall be put in circulation and the manner of keeping the percentages fixed? We have no idea.

Blood-plates.—Besides the red disks and leukocytes, we find in normal blood a varying number of small, colorless, nonameboid elements about 2 or 3 μ in diameter and of various shapes, oval being the commonest. They often cohere in masses which have been compared to bunches of grapes. No nucleus can be made out. Their staining affinities are not constant; some have affinity for acid, others for basic dyes. There are many reasons for supposing that these so-called blood-plates or blood-platelets form a group which includes elements of various origins, fragments of red and of white corpuscles making up the bulk of their number. In health they number from 200,000 to 300,000 per c.mm.

Plasma.—Of the healthy plasma, there is little to be said that falls within the scope of this article. The variations in the amount of fluid in the vessels are considerable, even within physiologic limits, as the experiments of Oliver have shown. Influences acting as vasoconstrictive increase blood-pressure and force out into lymph-spaces more or less plasma, so that the number of corpuscles in a given volume is increased. When the blood-pressure is temporarily diminished, fluid from the surrounding tissues enters the vessels and dilutes the blood, so that the count of corpuscles per cubic millimeter is lessened. Such results must not be attributed to any change in the number of the corpuscles themselves, but only as local or temporary concentration or dilution.

ANEMIA.

As above stated, anemia is in all probability a symptom of some deeper trouble, toxic or other. It is perhaps best defined as “a condition of deterioration of the blood, with altered relations of the fluid and solid parts” (Stengel).

This deterioration is generally manifested by changes in the serum, which are probably at the root of the alterations seen in the corpuscles. In the corpuscles themselves the manifestations of anemia are: Diminution in corpuscle substance, either through loss of corpuscles or through loss of hemoglobin in each corpuscle; various degenerative changes (poikilocytosis, polychromatophilia, etc.); presence of unripe corpuscles (nucleated red cells, myelocytes, etc.).

So far we have referred wholly to qualitative changes in the serum and

corpuscles and quantitative changes in the latter. Of the existence of a true and continuous insufficiency in the total quantity of blood, we have no direct proof, though it is believed by some to occur, and many clinical facts suggest it.

The term "anemic" or "ischemic," as applied to an organ, usually refers to a pallor due either to diminished bulk of blood in the organ or diminished amount of coloring matter in the blood then present. The term is often applied to patients merely because of pallor of the skin; but this may be extreme without there being any discoverable changes in the amount or quality of the blood, and is probably then the result of vasomotor conditions.

We may distinguish acute anemia from loss of blood and chronic anemia due to qualitative changes in the blood. The distinction of "primary" and "secondary" anemia has already been briefly discussed on page 45. It is not probable that this distinction will stand the test of time; but it has still a certain usefulness if applied simply to group together, on the one hand, the cases of the cause of which we *are* aware (secondary anemias), and, on the other hand, those in which the important etiologic factor is unknown (primary anemias).

Bearing this in mind, we may classify anemias as "*primary*," including chlorosis and pernicious anemia, and "*secondary*" (due to carcinoma, hemorrhage, bad hygiene, etc.).

The terms "simple primary anemia," "splenic anemia," and "secondary pernicious anemia" should be discarded. "Simple primary anemia" refers either to skin pallor, from which the inference of anemia is made without corroborative blood examination, or else to secondary anemia from bad hygiene, rapid growth, or the like.

"Splenic anemia" refers to the association of anemia with enlargement of the spleen. But, as there is no one type of anemia which may not be attended by splenic tumor, there is no definite reason for using the term.

"Secondary pernicious anemia," a term used chiefly by German writers, refers to conditions more or less like those found in pernicious anemia, but associated with a definite cause, like carcinoma or nephritis. This blurs over an important distinction, since the blood changes in such cases are markedly different from those found in true pernicious anemia. In two or three cases, a single small cancerous nodule at the pylorus has been found at autopsy in cases of pernicious anemia, but there is no reason to believe that such a nodule can cause such an anemia.

PERNICIOUS ANEMIA.

A very large number of causes have been frequently mentioned in connection with the disease. Syphilis, malaria, child-bearing, hemorrhage (especially repeated small losses of blood), nervous shock, chronic gastrointestinal diseases, and many other affections have been supposed to cause the anemia. The evidence as presented goes to show that these influences have no effect unless perhaps as the straw that breaks the camel's back.

Any of these causes may be followed (*a*) by no considerable anemia, (*b*) by a characteristic secondary anemia (*vide* p. 472), (*c*) by pernicious anemia. But the number of cases in which pernicious anemia follows one of these affections is so small that the sequence is in all probability accidental.

The only genuine cause with which we are acquainted is the action of intestinal parasites, especially the *Bothriocephalus latus* and the *Ankylostoma duodenale*. The symptoms and signs, including the blood condition in cases caused by these parasites and cured by their expulsion, may be *identical* with those found in the so-called idiopathic and fatal cases. It is true that there are many cases in which these parasites inhabit the intestine without causing any anemia; but the frequent instances of cure immediately following the expulsion of the parasite make it probable that the parasite is the cause, in the same sense that lead is the cause of many colics and paralyses.

This fact, together with recent observations as to the method in which these parasites impoverish the blood, give us such notions as we have respecting the mode of production of nonparasitic cases. There is every reason to believe that the parasites do harm, not by the amount of blood which they actually suck into themselves and consume, but through the influence of some poison which they produce in the intestine and which is thence absorbed into the blood. If recently discharged proglottids of *Bothriocephalus* are fed to animals, an anemia is rapidly produced. This suggests that non-parasitic cases may be due to an auto-intoxication with products absorbed from the gastro-intestinal tract, under conditions of which we are ignorant.

Pernicious anemia is by no means an uncommon disease. The writer has had the opportunity of studying 110 cases within the last eight years. Its geographic distribution, apart from the parasitic forms, is probably in direct proportion to the activity of medical science in any given district.

Age and Sex.—Persons between forty and sixty years appear to be more subject to the disease than those above or below these limits. It is rare under the age of twenty; the author has seen two cases in patients past their seventieth year.

Among the author's cases there was a slight preponderance of males. Thus, of 110 cases, 57 were males and only 53 females. The older statistics, which include many cases following parturition, show about an equal number in each sex. The rarity of cases following parturition in the more recent statistics makes the correctness of the diagnosis in older accounts doubtful.

Morbid Anatomy.—The unknown poison which is now generally believed to be at the root of pernicious anemia expends itself chiefly in three ways: (*a*) On the blood; (*b*) on the spinal cord; (*c*) on the parenchyma of the heart, liver, and kidney, where extensive fatty degeneration is the striking change.

Secondary to these in all probability come: (*d*) Hemorrhages in various organs and from serous surfaces and mucous membranes; (*e*) compensatory changes in the bone-marrow; (*f*) deposits of iron-containing pigment, especially in the liver; (*g*) atrophy of the gastric mucosa (in some cases).

The Blood.—Gross Appearances.—The *color* of the drop, as it emerges from a puncture, varies a great deal. In most cases it is very pale and watery-looking, though not more so than is occasionally seen in severe cases of chlorosis or secondary anemia. But not infrequently the color of the blood in gross is as bright a red as normal blood, even when not over one-fifth of the normal number of corpuscles is present. The color in these cases is probably due to the high hemoglobin percentage present in all of the cases in which bright-red blood is seen in pernicious anemia.

The drop often looks streaked and particolored, as if the cells were separating themselves from the plasma; this appearance may be seen in any severe anemia.

As striking as the color of the drop is its great *fluidity*. The rapidity with which it slips off the ear or finger makes it difficult to manipulate it (embryonic blood shows a similar property).

Coagulation is very slow.

The *specific gravity* is usually much diminished—*e. g.*, to 1.025 (normal, 1.058).

Red Corpuscles.—*Quantitative Changes.*—Most cases show 1,000,000 to 2,000,000 cells per c.mm. when they first come under observation. The fall of the count to this point is often very rapid; while beyond this the fall, if it occurs, is slow. There are evidently conditions which tend to arrest the destructive process at this point. Thus, of the 110 cases mentioned, 79 showed between 1,000,000 and 2,000,000 corpuscles per c.mm. when first examined. The other 31 counts were below 1,000,000. Of these 31, 8 fell below 500,000 corpuscles per c.mm. before death. The lowest count in the series was 363,000. The lowest on record was reported by Quincke twenty years ago—143,000 per c.mm.

In some cases the corpuscles remain at practically the same figure until death; others progressively decline. Most frequently, however, one or more remissions occur, in which the blood may become quite normal, but which are always followed by relapse. There may be as many as five such remissions before death finally ensues.

Hemoglobin.—In 71 per cent. of the cases, the hemoglobin percentage was relatively high—*i. e.*, the amount per corpuscle was increased, although the total amount was of course very low. This *relative* increase of hemoglobin is known as a *high color-index*. The color-index of normal blood being 1, that of cases of pernicious anemia may be as high as 1.7, while in most severe secondary anemias it is below 0.5.

In the remaining 29 per cent. of the cases, the color-index was low or normal, which means probably that these cases were improving when they were seen, since we not infrequently see a low color-index in periods of remission.

Qualitative Changes in the Red Corpuscles.—*Average Diameter.*—Usually the average diameter of the red corpuscles is increased. This was the case in 80 per cent. of the cases; in the remainder it was normal.

While the *average* diameter is increased, even in those cases where the largest forms of red cells (macrocytes) occur, there are always normal and small forms (microcytes) as well, though usually in smaller numbers than the large forms. Some of the latter may be as much as 20 μ in diameter, while the dwarf forms are sometimes barely 2 μ across.

Variations in Shape.—Very commonly, though by no means always, we find greatly deformed corpuscles in the blood; all but 12 of the cases showed these. In the 12 exceptional cases, some showed really normal shapes, while most of them exhibited only slight deformities. These deformities are in no way characteristic of pernicious anemia, but occur in all severe anemias.

Henry has called attention to the fact that many of the deformed corpuscles assume more or less of an oblong or *oval shape*. This, like the increase in size, may be interpreted as a tendency to regression toward the type of blood seen in lower animals (*e. g.*, in frogs).

A great number of other deformities are seen; battledore-shaped, pear-shaped, and star-shaped forms occur. In one case observed by the writer, all the corpuscles were sausage-shaped, looking at first sight like a lot of gigantic bacilli.

Ameboid movements in deformed red corpuscles are occasionally seen, either in the projecting points or in the corpuscle as a whole. They are usually slow, but sometimes so rapid as to remind one strongly of bacteria or animal parasites.

Rouleaux formation is often absent or slight.

Peculiar Staining Reactions.—As already mentioned, normal red corpuscles react readily to acid stains and feebly to basic ones. Stained with hematoxylin and eosin, they take up only the eosin; with Ehrlich's triacid mixture, only the orange G. In pernicious anemia, on the other hand, some of



FIG. 157.—Pernicious anemia: L, L, lymphocytes; m, m, megaloblasts; cover-slips stained with Ehrlich's triacid, and drawn with camera lucida.

the red cells may have their affinities so modified that they take up a mixture of acid and basic stains, becoming purple with eosin-hematoxylin and purplish brown with Ehrlich's stain. This condition is very frequently seen in nucleated red corpuscles. It is easily simulated by conditions due to faulty technic. Spots in the corpuscle may have a different staining affinity from the surrounding corpuscle, so that they can be counterstained.

Nucleated Red Corpuscles (Erythroblasts).—Long recognized as a feature of the blood in pernicious anemia, the importance of this form of immature corpuscle as something peculiar to the disease has been of late considerably obscured by the fact that cells in many respects similar are found in a great variety of secondary anemias, as well as in leukemia. This confusion has been mitigated in some degree by the differentiation of two subvarieties of nucleated red corpuscles, viz.: (1) normoblasts, (2) megaloblasts.

The former of these was identified especially with cases of secondary anemia (posthemorrhagic, postmalarial, cancerous, etc.), while the latter was

thought to be characteristic of pernicious anemia. Ehrlich insists especially on this distinction. While recognizing that normoblasts were occasionally found in pernicious cases and megaloblasts occasionally in secondary cases, he yet asserts that in pernicious anemia the majority of all the nucleated corpuscles present are megaloblasts, while normoblasts are relatively infrequent. In secondary cases, on the other hand, normoblasts predominate.

Normoblasts are described, by Ehrlich and others, as red cells of normal size, containing a small nucleus, which stains intensely; megaloblasts as much larger than normal, and possessing a very large, pale-stained nucleus. Ehrlich believes the latter form of erythroblast to be characteristic of the fetal type of blood formation, while the normoblast represented the normal adult method of blood regeneration. Hence it is the latter that is found in the blood after hemorrhage; indicating that in the rapid regeneration of red corpuscles called forth in the healthy marrow by the loss of blood, a few immature cells are accidentally pushed into the circulation before losing their nuclei.¹

When, on the other hand, we find megaloblasts preponderating in the blood, as in pernicious anemia, it points, according to Ehrlich, to a reversion to an earlier and less fruitful type of blood formation—the fetal type.

This division by Ehrlich of erythroblasts into normoblasts and megaloblasts, and the significance which he attaches to them, fit the facts perfectly in perhaps three-fourths of all cases. That is to say, in the great majority of all cases of secondary anemia, we find cells corresponding to his description of normoblasts, and very few if any megaloblasts; while, in most cases of pernicious anemia, we find that the number of normoblasts present is much smaller than the number of megaloblasts. Now and then, however, a case occurs which does not correspond with Ehrlich's description. We may find nucleated corpuscles not corresponding to either of Ehrlich's types. Indeed, the writer has seen one or two cases in which not one of the many nucleated corpuscles present could be classed either as a normoblast or a megaloblast. This fact has been interpreted by Askanazy to mean that the normoblasts are simply *old megaloblasts*, the same cell passing gradually from one form to the other. He scouts entirely Ehrlich's idea of two types of blood-formation and of the different prognostic significance of the two varieties. In this he has been followed by many recent German writers, especially those who have not personally examined the blood of many cases. But Schaumann, Thayer, and most of those who have first-hand knowledge of any considerable number of cases are convinced of the fundamental truth of Ehrlich's view as to the different prognostic import of the two varieties of erythroblasts. His idea of blood-formation by extrusion of the nucleus has been generally abandoned, but is not the main point of his doctrine. The recent studies of Pappenheim² have gone far toward vindicating Ehrlich's idea of the essentially different nature of normoblasts and megaloblasts. The apparent "transition" forms not classed under either rubric, he considers as the older or younger forms of one or the other variety. The small, dark, structureless nucleus characteristic of normoblasts is in fact a typical old nucleus, and the large pale

¹ Ehrlich supposed the nuclei of normoblasts to be extruded and then to give rise to new red corpuscles. Pappenheim has shown that this is not the case.

² *Inaug. Dissert.*, 1895, and *Virchow's Archiv*, vol. cxlv., 587-648, 1896.

nucleus with clear and delicate nuclear structure (Ehrlich's "megakaryoblast") is in fact a young nucleus.

As a rule, we find only *old* normoblasts and *young* megakaryoblasts, the latter being so fragile and vulnerable that their nuclei rarely grow to maturity; while the former, representing the stable adult type of blood-formation, are much more likely to mature before getting into the blood. Occasionally, however, we do find young normoblasts (*i. e.*, with large light nuclei) or old megakaryoblasts (*i. e.*, with relatively small dark nuclei), and thus the supposed transitional forms of Askanazy are accounted for. The real distinction between a normoblast of any age and a megakaryoblast of any age is really in the character of the nuclear network; and this is not ordinarily seen with the stains used for clinical or routine pathologic work, as described in this article. But as, fortunately for us, we seldom see anything but small old normoblasts and large young megakaryoblasts, and as the marks of age and size are fairly easy to make out with ordinary technic, we are quite safe in considering all overlarge cells with young nuclei as megakaryoblasts, and all small cells with old nuclei as normoblasts. For the atypical forms occasionally seen, we must fall back upon the size of the whole cell as the best guide in clinical work.

One hears now and then of cases of pernicious anemia with no nucleated red cells at all in the blood. It is not impossible that such a condition may exist for a day or two, but in the vast majority of cases a patient search will show a few nucleated forms at all times, and plenty of them most of the time. They were present in every one of the cases examined by the writer more than once (107 cases), although sometimes hours of search were needed to disclose them. All of Schaumann's 38 cases and of Billing's¹ 20 cases showed nucleated forms. The writer has never been able to see any correspondence between the severity of the case and the abundance or paucity of erythroblasts. In his cases the number has varied from 3 to 7100 per c.mm. of blood, or from 2 to 6500 in every 1,000,000 red cells.

Ehrlich describes a case of fatal posthemorrhagic anemia in which he could find no nucleated corpuscles whatever. Autopsy showed that no regenerative effort had been put forth by the bone-marrow (*vide infra*, p. 466). There was no transformation of yellow (fatty) marrow into red (lymphoid) marrow, such as is almost invariably the case after traumatic or experimental hemorrhage. According to Ehrlich, therefore, a scarcity of nucleated red cells in pernicious-anemia cases would indicate the same lack of response on the part of the bone-marrow as was demonstrated in this case of secondary anemia.

But be this as it may, the cases with fewest erythroblasts are not the most severe, nor are those with most numerous erythroblasts any milder in type. This does not necessarily contradict Ehrlich's hypothesis, since there is abundant evidence that it is not simply or even chiefly the lack of red corpuscles that does the mischief in pernicious anemia. One patient with only 500,000 corpuscles per c.mm. may be up and about and do some work, while another patient with 1,800,000 may die. *It is not the anemia that is pernicious.* The anemia simply reflects very roughly the deeper underlying disease.

As to the kind of erythroblast, the writer's cases have with a single

¹ *Transactions Assn. Amer. Physicians*, vol. xv., p. 332, 1900.

exception, all shown a great preponderance of megaloblasts over normoblasts, the proportion being about 4 to 1 on the average.

In the remissions of the disease, nucleated corpuscles disappear from the blood simultaneously with the deformed, oversized, and abnormally stained varieties.

On the whole, then, although the presence of nucleated red corpuscles usually indicates an appeal to the marrow for more corpuscles (anemia) and hurried or faulty production there on account of the increased demand, we must not let ourselves be carried away by any gross mechanic theory, such as that the nucleated forms are simply carried along into the blood by the rush of newly formed cells hurrying to the rescue of defeated comrades. For we not infrequently find nucleated red cells in the blood when there is no loss of red cells to be compensated, no anemia to be cured. Thus, Ehrlich reports the finding of large numbers of nucleated forms in hemorrhagic small-pox, acute phosphorus poisoning, and chloroform icterus, with no anemia; and in the early stages of many cases of leukemia, when no anemia is present, enormous numbers of nucleated erythrocytes are seen.

White Corpuscles.—A great diminution of the number of leukocytes is the rule in all severe cases. Frequently less than 1000 are found in a cubic millimeter of blood. This is the more striking because, in other varieties of severe anemia, the leukocytes are usually normal or increased in number. In the remissions of the disease, the leukocytes rise with the erythrocytes and often go above the normal figure.

The differential count of leukocytes shows usually a striking decrease in the polymorphonuclear neutrophiles, giving rise to a considerable relative increase in the lymphocytes. In one of the writer's cases the lymphocytes rose to 79 per cent., and in another to 71 per cent.; the average in 110 cases was 45 per cent. as against the normal 30–35 per cent. Usually this increase is especially in the smaller forms. The eosinophiles average about 2.5 per cent., practically normal. A notable feature of the blood of pernicious anemia is the nearly constant presence of small percentages of myelocytes. These cells were seen in 80 per cent. of the cases, averaging about 2 per cent. of the leukocytes present. They are also seen in severe secondary anemia and in leukocytosis from any cause.

Occasionally we see basophiles, lymphocytes with neutrophilic granulations, and other anomalous forms, of which further account will be given under leukemia. Blood-plates are greatly diminished.

So much for the morphology of the blood in pernicious anemia. The amount of water in the blood is greatly increased and the solid constituents diminished, although the reduction of the amount of albumen in the serum is less than might be anticipated. In this respect it contrasts with most cases of anemia due to hemorrhage or malnutrition, in which the serum itself is greatly thinned. The blood in pernicious anemia, then, is *not* hydremic in the sense that the serum is watery, but simply contains an increased amount of relatively normal serum.

The Central Nervous System.—The Brain.—The general tendency to the extravasation of small quantities of blood is especially marked in the brain and meninges. The clots organize and remain as pigmented membranous spots in the meninges; in the brain itself, the site of the hemorrhage is marked by a collection of pigment, with vacuolization, edema, and diminished affinity for carmin stains.

Changes in the Spinal Cord.—Practically every case of pernicious anemia shows lesions in the spinal cord postmortem, whether these have given rise to symptoms during life or not. Out of upward of 40 cases on record, the writer can find but one (that of Burr) in which no changes were discoverable. The association of anemia and spinal-cord lesions cannot, therefore, be considered accidental.

The distribution of the lesions is usually symmetric or nearly so. The portion of the cord especially affected is that occupying the cervical and dorsal regions; "the lesions progressively decrease in intensity and extent at lower and lower levels of the cord, until in the lumbar region there is no disease at all, or it is extremely slight" (Burr). There are occasional exceptions to this. The gray matter is usually unaffected, the favorite seat of the lesions being in the posterior columns, especially in Goll's and Burdach's columns. The disease may be confined to this locality, and it is almost always more severe there than elsewhere. In some cases the lateral columns in and

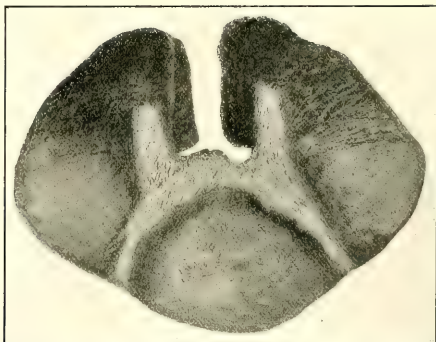


FIG. 158.—Section of spinal cord, upper dorsal region, from a case of pernicious anemia (Burr).

near the pyramidal tracts are also somewhat affected, and rarely the direct cerebellar tract as well. "Almost invariably there is a band of normal white tissue separating the diseased area in the posterior columns from the gray matter" (Burr). In the cervical region, there are often two separate areas of sclerosis within the posterior columns. No gross deformities or alterations in the shape of the cord are produced, the disease contrasting in this respect (and in its cervical localization) with tabes. Occasionally hemorrhages in the cord are found, as in the cases of Petion,¹ Lenoble,² and Teichmüller.³ The latter describes hemorrhage into the anterior fissure and numerous minute foci of blood in the gray matter, as well as in the anterior and lateral columns. This case also showed increase of neuroglia and thickening of the vessels and the usual degeneration of the posterior columns. Teichmüller inclines to the view that all the lesions are primarily due to hemorrhages. Nonne thinks that the earliest stages of the process consist of minute foci of acute myelitis.

¹ *Nord. Med. Ark.*, N. F., vi., 1896.

² *Revue de Méd.*, June 10, 1897.

³ *Deut. Zeit. f. Nervenheilk.*, viii., 1896.

Bastianelli divides the cord lesions of pernicious anemia into three groups: First, those occurring in rapidly fatal cases, where the nervous symptoms are slight or absent and are overshadowed by the symptoms of general anemia; such cases show irregularly scattered foci of degeneration, chiefly in the posterior columns, some in the lateral columns. Second, cases of slow clinical course, in which the nervous symptoms (paralysis, etc.) appear earliest, and later the anemia is noticed; in such cases the lesions agree with the suggestion of the symptoms and are more continuous and extensive. Third, cases in which the lesions are mainly due to multiple minute hemorrhages, as suggested by Teichmüller. "The condition is not systemic; that is, it is not confined to any one tract or set of tracts, but overlaps boundaries" (Burr).

The great majority of writers on the subject agree in considering the lesions as a manifestation of toxemia, and therefore similar to the lesions found in diphtheria, pellagra, ergotism, and diabetes.

This conclusion is the more natural in that it has been shown of late years that, despite the lack of red corpuscles, there is no lack of oxidation



FIG. 159.—Section of spinal cord, cervical swelling, from a case of pernicious anemia (Burr).

in the tissues. There is hyperoxidation rather than diminished oxidation, and no theory of oxygen starvation can be used to explain the cord lesions.

A very slight degeneration of the posterior peripheral nerve-roots is sometimes found, and in von Noorden's case the tibial and peroneal nerves also showed degenerative changes.

The histologic changes vary according to the age of the lesions. Those most recent show normal axis-cylinders with swollen and granular myelin sheaths and no changes in the interstitial substance. In the older portions, there is great increase of neuroglia and of nuclei with space-formation. The sheaths and axis-cylinders are shrunken or gone, and there is often a honey-combing of the tissue, the spaces being empty, or full of clear homogeneous substance. In the connective-tissue network, numerous corpora amylacea may be seen. The walls of the vessels may be thickened and hyaline.

Fatty Degeneration of Various Organs.—The heart shows extensive fatty changes in almost every case. As a whole, it may be so flabby that, if held by the apex in an upright position, it collapses so as to

cover the hand that holds it. The endocardium, particularly over the papillary muscles, shows a yellow mottling, the so-called tabby-cat or wren's-breast mottling. The changes are usually most marked on the papillary muscles of the left ventricle, possibly because this is where the greatest strain falls in the work of the heart. The whole organ is occasionally hypertrophied and dilated; but, as a rule, it is normal or undersized.

Under the microscope, the cross-striation and nuclei are gone; and in the place of the former, fat-drops are arranged in rows, "like pearls on a string." These changes, however, are not in any way peculiar to pernicious anemia; any variety of secondary anemia, even the acute posthemorrhagic types, may exhibit similar lesions.

The heart's blood is often found partially fluid many hours after death. A few pale, loose, friable clots may be found. The aorta is usually of normal size. Fatty degeneration of the capillaries, especially in the brain, may be extensive.

The kidneys are intensely pale throughout and uniformly yellowish. The capsule is not adherent. The organ is very soft and greasy. Microscopically intense fatty and granular degeneration is found, especially in the convoluted tubules. Small hemorrhage may be seen under the capsule or microscopically in the glomeruli. Deposits of pigment containing iron are occasionally to be found (*vide infra*).

The liver is sometimes enlarged, always very pale, and microscopically shows extensive fatty changes. The deposit of iron in the organ is mentioned on page 458.

The pancreas occasionally shows fatty degeneration.

These lesions were formerly attributed to suboxidation of the tissues, owing to the supposedly great diminution in the oxygen-carrying power of the blood. But, since it has been shown by von Noorden and others, as above mentioned, that the blood somehow manages to carry all the oxygen needed by the tissues,¹ some other explanation must be sought. While nothing positive is known as to the cause of the fatty changes, it is natural to suppose that they are similar to those occurring in diphtheria and in phosphorus or arsenic poisoning, thus bringing them into relation with the changes in the blood and spinal cord as the direct results of a common toxic cause.

Apparently there is no parallelism between the severity of the anemia and the extent of the fatty changes (Krehl).

Changes in the Bone-marrow.—While there is reason to believe that the fatty changes in the parenchyma of the organs, like the lesions in blood, stomach, and spinal cord, represent relatively direct effects of the unknown poison, the marrow-changes appear to be secondary or due to an effort at repair, such as causes hypertrophy of the heart after antecedent changes in the valves.

In a certain number of cases, no such changes are found; the marrow presenting at times no alterations at all, at times only such as are common to various chronic diseases. Cases in which no changes are found in the marrow are usually those in which clinically no nucleated red corpuscles appear in the blood, indicating an absence of effort at regeneration. Especially rapid cases sometimes show no marrow-changes.

When changes do occur, they consist macroscopically of a transformation of the fatty marrow normally found in the shaft of the long bones of adults,

¹ In health, apparently only part of the oxygen-carrying power of the corpuscles is used.

into red or "lymphoid" marrow, similar to that found in the epiphyses normally, or in the whole shaft in late fetal life. The red marrow is often compared to currant jelly, the consistency probably being in mind as much as the color, for in well-marked cases the marrow may be almost fluid. So far as gross appearances go, the marrow is identical with that found in any severe secondary anemia or after experimental bleeding in animals.

But microscopically we find what Ehrlich has termed "megaloblastic degeneration." In the red marrow of experimental anemia, the red color is due to the replacement of fat by red corpuscles, chiefly nucleated and of the normoblast type; that is, the diameter of both nucleated and nonnucleated forms is approximately normal. In pernicious anemia, on the other hand, the majority of the corpuscles are oversized and those with nuclei are of the megaloblast type (*vide supra*). Many of the nuclei show signs of karyokinesis, but in the majority the nucleus is in one of the conditions known as karyorrhexis and karyolysis; that is, it is breaking up or fading out.

While the average diameter of the red corpuscles is usually increased (as in the circulating blood), there is a very great variation in their size—*i. e.*, from 3 μ to 17 μ in diameter—and also in the amount of hemoglobin in the cell. In this respect, however, the conditions of the normal epiphyseal marrow are but slightly exaggerated; for we find there great differences in size and in the amount of hemoglobin in any red marrow. The writer always gets the impression, in examining such marrow, that he is in the workshop, where all stages of the unfinished product are to be seen.

The marrow-leukocytes are less numerous than usual, but not otherwise abnormal, except that the number of the giant leukocytes of the marrow is increased. Such cells often take up several red corpuscles. The amount of pigment in and between the cells is increased.

Red marrow may be present in spots or islets in the shaft of the bone, or may occur in the whole space. The tibia usually shows such changes well. Schaumann found they were absent in the ulna and radius of cases in which the humerus and femur showed them well.

Smear-preparations show the finer changes much better than sections. A drop of the semifluid marrow is spread between two cover-glasses in the manner explained above, and then heated and stained like a blood-film.

The spleen and lymph-glands show no changes, in the majority of cases. Now and then we meet with splenic enlargement, and the writer has twice seen this so great as more than to double the normal weight of the organ. The spleen is usually soft and the pulp increased in volume. Microscopically no changes of special significance, except a deposition of iron-pigment, are present.

Increase of Iron in Various Organs (*Siderosis*).—The liver, kidneys, spleen, and bone-marrow are the organs especially concerned; occasionally also the pancreas and lymphatic glands.

The amount of iron contained in the liver may be as much as 23 times the normal quantity. The iron-pigment is distributed chiefly in the cells of the outer and middle zones of the hepatic lobules. This distribution is believed by Hunter to be characteristic of the disease. Iron-pigment is also deposited in the leukocytes and the endothelium of the capillaries, but this is apparently of no special significance. The presence of the metal may

be demonstrated by a solution of ammonium sulphid, which, combining with the iron to form the black sulphid of iron, at once blackens the tissue. Liver sections can also be stained so as to exhibit very beautifully the distribution of the pigment, by being soaked for several hours in a solution of ferrocyanid of potash, and then in dilute hydrochloric acid for an equal time. The areas containing iron-pigment are stained blue (Prussian-blue reaction).

In the kidney, spleen, pancreas, and marrow, the increase of iron is much less marked than in the liver.

Atrophy of the Gastric and Intestinal Mucous Membrane.—

The changes in the secreting tubules are at times so marked that they have been supposed by some of the earlier writers on the subject to be the source of the other lesions—*i. e.*, to be the “cause” of the disease through inanition. But many cases show at autopsy no such changes, and in the vast majority there are periods of good digestion throughout the clinical course of the disease, such as could not exist if the digesting functions were destroyed or greatly impaired. It is much more likely that the atrophic condition of the gastro-intestinal mucous membrane which is found in a certain percentage of autopsies is secondary to the lesions already described.

The changes may be macroscopic or only microscopic. In some instances the whole gastro-intestinal tract shows a striking thinness, smoothness, and transparency; at times this is seen only in the stomach. In other cases the wall of the stomach is tough and opaque from interstitial hyperplasia.

Microscopically we may find: (*a*) Fatty degeneration of the secreting tubules; (*b*) complete destruction of epithelium, with reactive hyperplasia of the interstitial tissue; (*c*) the whole glandular mucosa may be gone, leaving only a lining membrane of flattened epithelium and reducing the thickness of the wall to one millimeter; (*d*) overgrowth of connective tissue in the mucous membrane and submucosa, especially the latter—its vessels may be thickened; the tubules are compressed and distorted as in ordinary interstitial gastritis; (*e*) Lubarsch found numerous eosinophile-cells and also masses of oxyphilic extracellular granules embedded in the interglandular tissues; (*f*) degeneration of the motor nerves of the intestine and of its muscular layer has been reported by several observers (Jürgens, Sasaki, and Blaschko). All these changes have been observed in diseases which run their course without extreme anemia—*e. g.*, mammary cancer, chronic lead poisoning.

Hemorrhages.—A striking feature of the autopsy of some cases of pernicious anemia is the presence of numerous punctate hemorrhages, seen especially on serous surfaces, as in the pericardium, but also on mucous membranes and in the skin. During life they are frequently observed in the retina. Their occurrence in the spinal cord has already been mentioned. Hemorrhage into the substance of the spleen is an occasional occurrence and may produce considerable enlargement of the organ. The cause of these various hemorrhages is unknown; they have been attributed, on insufficient evidence, to embolism and to degeneration of the capillary walls.

Other Changes.—The yellow color of the skin, so characteristic of the disease during life, is also very marked in most cadavers. It is a peculiar pale straw color, not unlike the tint of manilla paper, and very evenly distributed throughout the body. The bright lemon-yellow of the subcutaneous fat, as well as the amount of the latter, is often striking. Patients do not emaciate, provided they are able to take a fair amount of food, as some

of them do to the very last. In about one-third of the cases, considerable emaciation is seen, probably as the result of anorexia and poor assimilation of food; but in the remainder the fat-layer is well preserved and its color is near an orange tint. The bright-red color of the muscles also attracts attention in many cases.

Although it is probable that the altered color of the skin, fat, and muscles is connected in some way with altered blood-pigment from the destroyed red corpuscles, we have no positive evidence that this is so. The colors are in no way the result of simple bloodlessness, which causes only pallor of the affected parts. This pallor is very striking in the lungs and stomach and is noticeable in all the organs.

Summary.—*Relatively primary changes:* (a) Great oligocythemia, with high color-index, enlarged and nucleated erythrocytes, no leukocytosis; (b) sclerosis of the posterior and lateral columns of the spinal cord; (c) fatty degeneration of various organs, especially of the heart. *Relatively secondary changes:* (a) Megaloblastic degeneration of the bone-marrow; (b) increase in the amount of iron in the liver and elsewhere; (c) atrophy of gastric and intestinal mucous membrane; (d) punctate hemorrhages in serous membranes and elsewhere; (e) pallor of all organs, discoloration of skin, fat, and muscles.

CHLOROSIS.

Definition.—A disease occurring exclusively in young women, usually between the seventeenth and twenty-third years, characterized by symptoms of anemia and by a great reduction in the amount of hemoglobin in the red blood-corpuscles.

Etiology.—Despite the frequency of its occurrence and the great activity of speculation concerning it, we are entirely ignorant of the real cause of chlorosis. Probably no disease has ever called forth a greater number or variety of unsatisfactory hypotheses. It has been attributed to changes in the gastro-intestinal organs, such as auto-intoxication from constipation, deficient formation of hemoglobin in the intestine, gastroptosis, dilated stomach, etc. (Clark, Forchheimer, Meinert, and Pick). Theories of a nervous origin are common, either referring the disease to mental or nervous shock, strain or overexertion, or looking upon it as a neurosis of the vasomotor and sympathetic nervous system. Vascular hypoplasia, especially of the aorta, has been supposed to cause the trouble (Virchow). Genital anomalies or disturbances in the function of the genital organs have been thought to be of etiologic significance (Rokitansky, Trousseau). Chlorosis has been considered an infectious disease, owing to the occasional slight enlargement of the spleen and occurrence of fever. Hayem and the French school generally stick to the theory that chlorosis is due to a lack of development of the hematoblasts (for such Hayem considers the blood-plates to be) into red corpuscles. Bunge's theory of iron-starvation through a combination taking place between the iron of the ingested foods and the sulphur of abnormal intestinal fermentation is exceedingly ingenious, but has been conclusively disproved, since there is no evidence of any abnormal intestinal fermentation.

Without enlarging this list of conflicting theories any further, we may now point out some of their difficulties. The constipation theory will not explain the cases, not at all rare, in which no constipation exists. Intestinal

fermentation is not greater than normal, as Räthen and Mörner have shown; gastropstosis is present in only about one-third of the cases, and dilated stomach still less often. Many cases arise without any nervous shock or strain whatever, and the evidence of a neurosis as part of the disease does not tend to show that this is the cause of it. Hypoplastic arteries are often found at autopsy where no chlorosis existed; and the use of iron, while curing the disease, cannot be supposed to enlarge the aorta, as it should if small vessels caused the disease. Genital anomalies are present in only a moderate percentage of cases; and, where present, no reasonable connection has been shown between them and the disease itself. Evidence of infectious origin (enlarged spleen and fever) is absent in most cases.

Hayem and his school stand alone in their belief that red cells are developed from blood-plates; but many modern observers hold the belief that defective hemogenesis is the cause of the disease. No evidence of increased hemolysis, such as can be shown in pernicious anemia, exists in chlorosis; and the corpuscles bear, as we shall presently see, some marks of being defective from the start.

Why the hemogenetic power is deficient, and what the connection is between the defective blood-making and the particular age and sex at which the disease occurs, are questions to which no answer can as yet be given. It has been suggested that the age at which the disease occurs corresponds to the "interregnum" between the end of the functional activity of the thymus gland and the establishment of the function of the ovaries, and that the absence of the influence of one or another of these organs is deleterious in some way to the organism and the blood. But chlorosis usually begins several years after the establishment of the menstrual function, and castrated women do not become chlorotic. The thyroid gland has been observed to be enlarged and sometimes tender in chlorosis, and some connection with the symptoms has been assumed to exist.

Biernacki has recently pointed out that too much stress has been put on the lack of hemoglobin, in our conception of the disease. The severity of the cases is not in proportion to the lack of hemoglobin, and the amount of iron in the blood is often normal.

In conclusion, it may be said that any satisfactory theory of the nature of chlorosis must take account of the following facts: That it is usually curable by the use of iron, hence it cannot depend on any gross anatomic lesion; that it is closely connected in some way with the period of life immediately following the establishment of the menstrual function; that the blood-changes do not differ essentially from those of many cases of ordinary symptomatic anemia and are not directly proportional to the severity of the symptoms.

Pathologic Anatomy.—Autopsies are so rare that but little is known of the lesions of chlorosis, all the less because in the few recorded autopsies there has been very little to see. We will begin, therefore, with the tissue the pathologic changes of which we can follow during life, viz.:

The Blood.—I. *Gross changes.*—In some cases, if a vein be punctured, blood will spurt from it as from an artery; and in many cases we note how very easily the blood flows from a needleprick. The pallor of the drop is often as great as or greater than in pernicious anemia. Coagulation is rapid, although the amount of fibrin is usually not increased. Many writers believe that the blood-mass is increased ("plethora serosa").

The specific gravity is always reduced and is in direct proportion to the reduction in hemoglobin.

II. *Microscopic Changes.*—(a) *Quantitative Changes.*—The number of red corpuscles in early cases is normal or approximately so; only in neglected cases, when the anemia has been allowed to progress untreated for a considerable time, does the count of red cells fall considerably. In neglected cases of long standing, we occasionally see very low counts. Stengel records one of 1,500,000 per c.mm. The lowest in the writer's experience is 1,932,000. Of 77 cases of which he has records, only 11, or one-seventh, showed a reduction of red cells below 3,500,000. On the other hand, it is not at all infrequent to see an actual increase. The writer has counted cases with 7,100,000, 5,884,000, and 5,620,000 red corpuscles to the cubic millimeter. The average count in his series was 4,050,000, and in Thayer's 4,096,544.

Hemoglobin, on the other hand, was reduced in the writer's series to 41 per cent. on the average; in Thayer's cases it averaged 42.3 per cent. Six of the writer's cases had less than 20 per cent. of the normal amount of hemoglobin (Fleischl). The color-index averaged 0.50—in striking contrast with that of pernicious anemia (1.04 in the writer's cases).

If any diminution in the number of red cells occurs, it takes place subsequently to the fall in the percentage of coloring matter; and conversely, in convalescents, the number of corpuscles reaches normal before the hemoglobin, as is the case in all anemias.

White Corpuscles.—There is no leukocytosis in the great majority of cases; the average count in the writer's series was 7485, and only one-tenth of the cases showed any increase. Rarely there is a slight temporary increase, especially during rapid convalescence.

The blood-plates are always increased.

(b) *Qualitative Changes.*—Hayem was the first to notice that in severe cases the diameter of the red cells is usually less than the normal—*i. e.*, 6–7 μ , instead of 7.5 μ , the normal. In mild cases this change does not occur.

The shape of the corpuscles is usually unaltered, although in marked cases poikilocytosis may appear and even reach an extreme grade. In fresh or stained specimens the lack of coloring matter makes the centers of the corpuscles strikingly pale, so that only the rim appears colored.

Nucleated red corpuscles are found only after prolonged search, and then sparingly. Almost invariably such nucleated corpuscles as do occur are of the normoblast type; but it is on record that megaloblasts have been once seen by Hammerschlag and once by Ehrlich.

The white corpuscles usually show a marked decrease, absolute as well as relative, in the number of polymorphonuclear cells, with a relative increase of the lymphocytes, especially of the smaller forms. Eosinophiles are occasionally slightly increased, and in severe cases we may see a few myelocytes, as in any other severe anemia.

Attempts have been made to distinguish a myelogenous and a lymphatic form of the disease, but the distinction has not been established.

Chemically the blood shows an increased proportion of water, although the dried residue of the serum is practically normal in amount. The amount of albumin is always decreased, as are the phosphorus and potash.

Other Lesions.—The hypoplastic heart and aorta are passed down from

book to book as a lesion of chlorosis, on the basis of the older observations, although the number of recent cases in support of it is trifling. In some cases there is slight cardiac hypertrophy, which has been explained in various ways. The aorta is usually said to be thin, narrow, and elastic, with areas of fatty degeneration of the intima and irregular origin of the intercostal branches. Similar conditions are often seen where no chlorosis is present.

One certain fact concerning the circulatory system is the marked tendency to thrombosis, especially of the cerebral sinuses, less often in the veins of the extremities. Thrombosis practically never occurs in pernicious anemia; on the other hand, hemorrhages—retinal or other—are very rare in chlorosis. The weakness of the circulation is shown by the frequency of slight edema of the ankles.

The *genital organs* are not infrequently hypoplastic or infantile, the uterus and ovaries being small and undeveloped, the number of Graafian follicles deficient, the fundus of the uterus disproportionately small, the breasts undersized, the pubic hair deficient. On the other hand, the genitals may be quite normal and are sometimes even hypertrophied.

The blood-making organs show no distinctive changes; the spleen may be slightly enlarged.

In extreme cases, fatty changes in the liver, spleen, and pancreas have been noticed. Gastropptosis or general enteropptosis occurs in about one-third of the cases, and the stomach may be dilated. The gastric contents show various anomalies of secretion, hypersecretion being the commonest.

Summary.—Such lesions as have been noted in connection with chlorosis have probably no essential relation to it. Of its real pathology, as of its real etiology, we are entirely in the dark. The blood changes are well marked, but not in themselves distinctive; for, though strikingly different from those of pernicious anemia, they may be identical with those of symptomatic anemia due to well-known causes.

SECONDARY ANEMIA.

Etiology.—The most important etiologic factors are: Hemorrhage; malignant disease; chronic suppurations; nephritis; dysentery; cirrhosis of the liver; acute infectious diseases and syphilis; poisoning (lead, arsenic, bad air, intestinal parasites); pregnancy and lactation; blood destruction (malaria, poisoning by chlorate of potash, by phenacetin, etc.); Addison's disease; myxedema; rickets.

The Blood.—The red corpuscles may be greatly diminished. The most extreme diminutions are seen in malignant disease, chronic malaria, syphilis (congenital or acquired), rickets, and after typhoid fever. The corpuscles in such cases may fall to or below 1,000,000 per c.mm.; but such low counts are the exception and not the rule. In most cases of malignant disease or phthisis, at the time of death the corpuscles are not greatly reduced and the changes in the blood affect chiefly the quality and not the number of the erythrocytes.

The condition of the blood typical of the vast majority of moderately severe cases is precisely that seen in chlorosis, so far as the red cells are concerned—*i. e.*, there is a reduction in the albumin and hemoglobin per cell, the total count remaining approximately normal or being even somewhat

increased. One gets the impression in many cases that the total blood-mass is diminished; but this is not susceptible of verification, as a rule. The reduction in hemoglobin, though usually present, is often surprisingly slight, considering the pallor of the patient.

In severe cases the corpuscles may be deformed and undersized. An increase of the average diameter, such as appears in pernicious anemia, the writer has never seen.

Nucleated corpuscles may be present in any form of secondary anemia, but are usually found only after long search, except in the anemias of infancy, where they are relatively frequent. In most cases only normoblasts are found. Rarely megaloblasts are seen, always in smaller number than the normoblasts. Karyokinesis and karyolysis may be observed. The abnormal staining reactions described under pernicious anemia are less marked in secondary anemia, but do occur.

Leukocytes.—Leukocytosis may or may not be present. After hemorrhage, in most cases of extensive new growths, advanced phthisis, or other suppurative processes, the white corpuscles are usually increased, the increase taking place chiefly in the polymorphonuclear forms. The latter may be relatively increased, even where no leukocytosis is present. In rickets the mononuclear cells may predominate, and this is not infrequently seen after hemorrhage and rarely in malignant disease. In the latter the eosinophiles sometimes show a relative and absolute increase. Small percentages of myelocytes are frequently present.

The alkalinity and specific gravity of the blood are usually decreased, and the amount of water is proportionately increased. Potassium is decreased and sodium increased. Iron, according to Biernacki, is not reduced.

LEUKOCYTOSIS.

Leukocytosis is an increase of the number of leukocytes in a given quantity of peripheral blood, over the number normal for the individual concerned, this increase never involving a relative diminution in the number of the polymorphonuclear varieties, and usually a marked absolute and relative increase.

The element of time insisted on by Fitz and others is of no importance, as the leukocytosis may persist for years or only for a few minutes.

The above definition needs some explanation: it says "of the peripheral blood" to avoid deciding the disputed point whether leukocytosis may sometimes mean an actual increase of the leukocytes in the body, or whether it is always a migration toward the periphery from the internal organs; whatever is the truth, the number of cells in the peripheral blood is certainly increased. The number of leukocytes normal for the individual must be previously known or calculable—a normal child of four years has a sufficient number of leukocytes per cubic millimeter to constitute a leukocytosis for an adult whose normal count is lower; different adults also differ more or less from each other. We must include in our definition a statement of the kind of leukocytes the increase of which constitutes leukocytosis in contradistinction from leukemia (lymphatic or myelogenous), lymphocytosis, and eosinophilia. It is not the number, but the kind, of leukocytes present that enables us to distinguish leukemia from leukocytosis; the count of leukocytes in bubonic plague or in sarcoma or in pneumonia may be greater than in leukemia, but

the increase is made up by cells of a different variety. Lastly, in order to be sure that the polymorphonuclear cells are not decreased, we must know whether the patient is a child or adult, since the normal relative proportions of the different leukocytes are very different in the infant and in the adult.

Leukocytosis may be (a) physiologic, (b) pathologic.

Physiologic leukocytosis occurs in the newborn; during digestion; during pregnancy, parturition, and the puerperium; after violent exercise, massage, electricity, brief cold baths, prolonged hot baths; in the moribund state (terminal leukocytosis).

The following table, compiled from the best authorities and from personal observation, illustrates the leukocytosis of the newborn:

Age.	Leukocytes.
At birth	17,000-21,000 (26,000-36,000 after first feeding)
End of first day	24,000
End of second day	30,000
End of fourth day	20,000
End of seventh day	15,000
Tenth day to about the tenth year	12,000

Digestion leukocytosis is present in most healthy individuals after a proteid meal, reaching its maximum in about three hours. The count is increased about 33 per cent. over the normal number. The normal percentages of the different varieties of leukocytes may remain the same, or there may be an absolute and relative increase of the lymphocytes. In gastric cancer and other chronic gastric trouble, digestion leukocytosis is usually absent.

Most primiparæ show, during the later months of pregnancy and after parturition, a leukocytosis of about the same extent as the digestion leukocytosis. It reaches higher figures at the time of parturition (often 15,000-20,000), and persists, as a rule, for at least a week afterward. The neutrophils alone, or all varieties of leukocytes, may be equally increased.

A number of influences acting on the vasomotor system, such as exercise, massage, and baths, raise the leukocyte-count about 33 per cent.

Near the end of many chronic diseases the leukocyte-count rises rapidly. This is especially marked in pernicious anemia, and may give rise to the mistaken idea of a transition to leukemia.

Pathologic leukocytosis may be divided as follows: Posthemorrhagic, inflammatory, toxic, and due to malignant disease or to therapeutic or experimental influences.

Posthemorrhagic leukocytosis may appear immediately after a hemorrhage or not till twenty-four hours or more have elapsed. It is moderate in degree (15,000), and may be a true leukocytosis or a lymphocytosis (*vide infra*).

Inflammatory leukocytosis appears associated with inflammations of all kinds, when neither the infection nor the resistance of the organism is easily victor in the struggle. The leukocytosis is of greater extent in virulent processes, whatever their cause and whether extensive local lesions are present or not. The count in severe cases of pneumonia or peritonitis may run as high as 100,000 per c.mm., 90-95 per cent. being usually of the polymorphonuclear variety.

Toxic leukocytosis is seen in such affections as illuminating-gas poisoning, uremia, ptomain poisoning (decayed fish), blood destruction (through the influence of free nuclein), quinin poisoning, during etherization, in gout, etc.

Most cases of extensive malignant disease, of whatever nature and situation, are associated with leukocytosis. Small growths, such as carcinoma of the stomach or the lip, do not produce, as a rule, any increase of leukocytes.

Salicylates, antipyretics, pilocarpin, nuclein, tuberculin, spermin, ergotin, injections of normal salt solution, and many other therapeutic measures raise the leukocyte-count.

An important group of infectious diseases is distinguished from all other infections by *not* producing leukocytosis. These are: Typhoid fever, malaria, influenza, measles, tuberculosis (unmixed infections, except meningeal cases), leprosy.

In typhoid fever, miliary tuberculosis, pernicious anemia, and many cases of malaria, the leukocytes are diminished.

Lymphocytosis.—This is a relative or absolute increase of lymphocytes in the peripheral blood. The condition is physiologic in infancy; and in many diseases of infancy, especially in those affecting the gastro-intestinal tract, it becomes very marked.

Rickets, syphilis, scurvy, some cases of malignant disease, chlorosis, pernicious anemia, chronic malaria, and other causes of cachexia may produce lymphocytosis. It may be seen after hemorrhage and in any condition of marked debility.

Eosinophilia.—This is a relative or absolute increase of eosinophiles in the peripheral blood. It is found in trichinosis and other diseases due to animal parasites, such as malaria, beriberi, ankylostomiasis; in bronchial asthma after tuberculin injections; in certain cases of sarcoma and in osteomalacia; in pemphigus, pellagra, dermatitis herpetiformis, and other skin diseases.

Theories of Leukocytosis.—The majority of modern writers agree in regarding leukocytosis as a manifestation of chemotaxis. A new production of cells can hardly be supposed, considering the rapidity with which the increase may appear and disappear. It probably represents a drawing-forth of the wandering cells from the capillaries of the internal organs, especially the bone-marrow. It is often preceded by a short period of diminution of leukocytes, or "leukopenia," in the peripheral circulation, during which time the cells heap up in enormous quantities in the lungs and other internal organs and are destroyed in considerable number, as maintained by Löwit. The occurrence of leukocytosis without inflammatory exudation upsets von Limbeck's theory that it forms a part of the process of emigration; and the fact that it does not occur in typhoid fever and it affects chiefly the polynuclear cells, and not the lymphocytes, disposes of Virchow's idea that it is due to stimulated glandular activity.

The prevalence of polynuclear cells is usually explained as due to their ameboid activity, which makes them quick to respond to chemotactic influence; but in many leukocytoses the polynuclear cells differ markedly in type from those seen in normal blood, and, if ameboid motion determined their migration to the surface, the eosinophiles, which are even more actively ameboid, should also increase.

To the mind of the writer, no theory of leukocytosis yet advanced suffices to explain all the facts.

LEUKEMIA.

The present state of our knowledge of this baffling and mysterious disease is perhaps best conveyed by considering it as characterized by the

presence in the blood and in the organs (in the form of tumors or irregular accumulations) of enormous numbers of leukocytes, either in the stage just before division ("theilungsreif") or just after division (small lymphocytes).

Under this general type there are recognized three subvarieties, each with a characteristic condition of the blood and of the organs—characteristic, that is, in being distinguishable from one another and from all other diseases except Hodgkin's disease. These three varieties of leukemia are: Chronic myelogenous leukemia (myelocythemia); chronic lymphatic leukemia (chronic lymphemia); acute lymphatic leukemia (acute lymphemia, lymphogonemia).

The first is characterized by the presence in the blood, in the nodules of the spleen and liver, of elements corresponding in morphology and relative proportion to the elements of the marrow; in the marrow the normal cells are greatly increased in number.

In the second, the blood, blood-making organs, and secondary nodules are flooded with elements corresponding to the small lymphocytes of normal blood and lymph.

The third shows chiefly a heaping-up in the blood, marrow, lymphadenoid structures, and visceral nodules, of cells corresponding to those seen normally in the germ-centers of the lymph-glands and to the large lymphocytes of the blood. These cells are lymphocytes ready for division ("theilungsreif"). Benda applies to them the term "lymphogonie." Following this terminology, we might call the condition of the blood "lymphogonemia."

Intermediate varieties, especially between the second and third of these divisions, are not infrequently observed. The more acute the case, the more nearly does it preserve the type described in the third division.

Causation and Pathogenesis.—As to the primary cause of the disease, we are utterly in the dark. All we know about it is that it results in a great acceleration of the process of cell division among the leukocytes and increased facilities for the entrance of the leukocytes so produced into the circulating blood. Without this last factor we have no leukemia, but only a pseudoleukemia (Hodgkin's disease).

The question as to whether the disease is primarily one of the blood, and secondarily of the blood-making organs, or *vice versa*, is generally decided in favor of the second view by the fact that mitoses are found almost exclusively in the organs, and only exceptionally in the blood. This is taken to show that the process does not originate in the blood, but that the blood-making organs are relatively the primary seat of the process.

That the unknown stimulus which excites these organs to greater activity is in all probability brought there in the first place by the blood or lymph, and does not originate in the organs themselves, does not prevent us from thinking of the blood as a secondary feature so far as the actual production of the new leukocytes is concerned. There is no good reason for supposing that the leukocytes are formed in the blood and carried thence to the "blood-making" organs; all the evidence points the other way. But, as has been pointed out by Müller, Hindenburg, and others, the capillaries of the liver and the lymph-passages of lymphoid organs are in leukemia great breeding-places for leukocytes. Probably a far larger number is produced here than in the germ-centers of the lymphoid organs themselves. These "breeding-places" may be said to stand midway between the freely circulating blood and the relatively solid and static tissues of the lymphoid organs. Such a stimulus has been somehow applied to the leukocyte-producing process that it

will go on in any slowed circulation, such as in the liver-capillaries, although the still slower circulation of the marrow and other lymphoid organs can also furnish the requisite conditions for cell division, and even in the rapid peripheral circulation mitosis occasionally occurs.

It has already been said that we rarely find in the blood or in the other tissues any relative excess of those cells which are usually considered more or less mature (polymorphonuclear neutrophiles, eosinophiles). Hence it has been supposed by some that the increased number of the other (young?) varieties was due in part to a delayed metamorphosis of the cells produced, as well as to an overproduction. That there is an increased production there can be no reasonable doubt; but whether or not the factor of retarded development plays a part, we are not as yet in position to decide. The great rapidity of cell destruction (witnessed by the increased uric acid in blood and urine), without decrease and often with increase of the leukocytes in the blood, would make it somewhat unlikely that the life of the individual cell is prolonged; and the large amount of leukocyte debris seen in all the organs is also against a prolongation of cell life. Such prolongation could at best account for little increase, since the supposed "mature" forms are absolutely much increased in some types of the disease, although hardly ever relatively increased.

As said above, there is nothing known as to the nature of the stimulus which produces such abnormal activity of the blood-making organs. It has been supposed to be of an infectious nature; but the great majority of cultural experiments have been negative, and where positive the result is to be explained as an accidental invasion of the diseased tissues by organisms irrelevant to the causation of the disease itself. The questions regarding the increased facility with which leukocytes enter the blood is discussed on page 475.

As with pernicious anemia and chlorosis, the opinion is gaining ground that the blood changes, although characteristic and of great diagnostic value, are not what weakens and finally kills the patient; for the clinical severity of the cases is not parallel to the extent of the aberrations of the blood from the normal. The same is, however, to be said of the changes in the blood-making organs. They are not proportional to the clinical severity of the case; and patients with huge spleens, extensive blood changes, and presumably equally extensive gland and marrow lesions, sometimes feel perfectly well and live for two or three years, or until carried off by some intercurrent disease. Nothing is more striking than the utter disproportion between the clinical mildness of many cases and the extensive alterations of the blood, the disease often being discovered by accident when the individual feels perfectly well.

The conventional divisions of cases of leukemia into lymphatic, splenic, and myelogenous, or into lymphatic on the one hand and splenomyelogenous on the other, are no longer justifiable. There are probably no cases confined to any one, or even any two, of these three sets of organs. Probably in all cases, and demonstrably in many, the whole lymphadenoid apparatus, including the spleen and marrow, is affected. The spleen is largest in chronic cases; and most, though by no means all, chronic cases are associated with the prevalence of marrow elements in the blood and elsewhere. But the spleen may be as greatly enlarged in cases of chronic lymphemia where there is no prevalence of marrow elements, and no one any longer

supposes that there are any peculiar cells coming to the blood from the spleen. The spleen forms part of the lymph-apparatus; and though it doubtless has various other functions besides the production of lymphocytes, the same could be said of the lymph-glands, which surely are not confined to this function. That the marrow also serves as the breeding-place of lymphocytes has been thoroughly established by the researches of Arnold, Neumann, and others, though the conditions here are not nearly so simple.

In the normal lymph-glands we find, at the germ-centers, large lymphocytes ready to divide; round them, large masses of small lymphocytes ("daughter-cells"); and in the lymph-sinus, polymorphonuclear cells.

In the normal marrow we find: (a) Lymphocytes, large and small. (b) Polymorphonuclear neutrophiles of all sizes, some very small; these are chiefly in the marrow-veins. (c) "Myelocytes" or mononuclear neutrophiles; these are the commonest of all varieties in the marrow, and are of all sizes, like the lymphocytes in the lymph-glands. (d) Eosinophiles—mononuclear or polynuclear, and of all sizes. (e) Basophiles, both finely and coarsely granular (γ and δ granulations). (f) Since the young granules have often different staining affinities than the older ones, it is often possible to find, in the marrow, cells containing granules of different tints.

Now, all these varieties may be found outside of the marrow in healthy persons (*e. g.*, in the intestine or peritoneum) except the mononuclear neutrophiles, which accordingly we are right in calling "myelocytes" or marrow-cells, despite the fact that so many other varieties may also be found there. Under pathologic conditions, myelocytes are found outside of the marrow, in the blood, the secondary lesions, and in various organs, and the condition may accordingly be called myelemia or myelocytthemia.

So far as any organ can be referred to in connection with one or another type of leukemia, we have (1) the myelogenous cases on the one hand, in which the lesions are chiefly or primarily of the marrow type, or in which the changes in other organs suggest the appearances of the bone-marrow; and on the other (2) the lymphadenoid type, in which the marrow, like the other organs, takes on the appearance of lymphoid tissue, while the spleen and glands show the most marked changes. This, however, does not account for the great enlargement of the spleen in myelogenous cases, which accordingly remains an unexplained fact. It is probably wiser to classify the cases of leukemia by their duration and the nature of their blood changes.

The influence of the factors usually mentioned in discussing the etiology of the disease is so slight, if it exists at all, that it may be dismissed with a word. The number of cases in males is greater than in females; the extremes of infancy and old age are seldom affected. Race, general environment, and the influence of other disease is of no importance. Inheritance may play a part. Transition from pernicious anemia or from Hodgkin's disease to leukemia are said to have occurred, but the writer has never seen such a case nor any satisfactory account of one.

CHRONIC MYELOCYTTHEMIA.

The drop, as it exudes from the puncture, is sluggish in its flow, and on close observation has a slightly opaque look; but in none of the cases which the writer has seen has there been any of the chocolate color or whitish appearance mentioned by so many writers. The partially clotted blood is

sometimes of these hues, and it is probable that the postmortem appearances have unduly influenced the descriptions of the living blood.

In early cases the specific gravity is very high, 1070 or even more; later, when anemia supervenes, it may fall as low as 1036.

Coagulation is slow, and there may be a hemorrhagic tendency. The alkalinity is diminished.

Microscopic Appearances.—Red Corpuscles.—Cases seen within six months of the first symptoms usually show no anemia whatever. Their red cells are normal in number, and their hemoglobin is up to par. This may continue for a year or more; and in cases where death is due to some complication (such as apoplexy or pneumonia), there may be no anemia at any time during the disease.

This is important, as many writers still speak of the disease as if it were a variety of anemia; and many clinicians would not consider leukemia possible in the rosy, vigorous patients in whom the writer has repeatedly seen it occur. It is also fatal to the old theory that the disease is due to the transformation of red into white corpuscles, an idea suggested by the fact that in later stages of the disease the constantly increasing white-cell count is accompanied by a gradual diminution of the erythrocytes.

It is true that, as the disease progresses, we find toward its close a marked secondary anemia, especially in prolonged cases where death is due to gradual exhaustion. Diarrhea, ascites, and other complications are often responsible for all or part of this anemia; occasionally the red cells may reach 1,000,000 or even lower before death.

The red cells show in such cases the deformities, altered chemical affinities, and lack of albumin and hemoglobin characteristic of all severe anemias. But perhaps the most interesting point about the red cells in this type of the disease is the presence of large numbers of nucleated red corpuscles, even when no anemia whatever is present. In the early stages of the disease, when the patient feels perfectly well and there is no reduction in the red corpuscles, we often find enormous numbers of nucleated red cells, more than in the severest types of anemia. As the disease progresses and anemia supervenes, the nucleated corpuscles do not increase in number. They are usually present in every microscopic field from the very first. The commonest type is the normoblast, the nucleus frequently being in a condition of karyorrhexis or karyolysis; but megaloblasts and microblasts are also seen.

The presence of these nucleated red cells shows that there is no necessary connection between them and anemia, and also gives us additional evidence of the importance of the bone-marrow in the disease. In lymphemia there is no such appearance of erythroblasts; indeed, they may be entirely absent, and, if present, are proportional to the grade of anemia.

Accepting the theory that this form of leukemia is due to a hyperactivity of cell formation in the bone-marrow, combined with an increased perviousness of the passages through which the cells are ordinarily sent out from the marrow into the blood, it is easy to understand how nucleated red cells might escape into the blood along with the myelocytes and other cells which are normally retained for further development. This certainly seems a plausible explanation of their presence.

Leukocytes.—On the warm stage, ameboid leukocytes are less numerous and less active than is usual or than in leukocytosis, owing to the presence of nonameboid myelocytes.

Quantitative Changes.—In the 38 cases of which the writer has notes, the average count of leukocytes at a comparatively early stage of disease (three to eight months from the first symptoms) was 430,000 per c.mm. The highest count in the series was 1,072,222, and the lowest 98,000. In the late stages they have been found even more numerous than the red corpuscles, but the highest ratio in the writer's series was 1 white to 2 red, the average ratio in 38 cases being 1 : 7 (normal, 1 : 750).

As the disease progresses the number of leukocytes usually rises slowly ; but remissions occur, with or without therapeutic influence, in which the count may actually fall to normal, and this may persist for weeks or even months. Further, the count may vary 30,000–50,000 in either direction from day to day without known cause.

The development of an intercurrent infection during the course of leukemia of this type is rarely without some marked effect on the blood. In the great majority of cases the count falls sharply, *e. g.*, from 400,500 to 89,000 (Herrick), from 246,000 to 57,300 (H. F. Müller). The nature of the infection (grip, pneumonia, miliary tuberculosis, erysipelas, etc.) plays no important part ; the effect is the same.

Rarely, as in one of Müller's¹ cases, the count may rise considerably—*i. e.*, from 180,000 to 400,000—and there is one case on record in which infection (acute articular rheumatism) produced no effect on the blood (Richter). Goldschneider found that by the injection of splenic extract or other substances he could bring about a diminution of the leukocytes, like that due to acute infections—without, however, bettering the patient's condition.

Qualitative Changes.—Polymorphism.—In normal blood we find the varieties of leukocytes pretty sharply differentiated one from another. Transitional forms are relatively rare, and it is not difficult to determine the relative percentages of the different elements. In the form of leukemia under discussion, the opposite is the case. The first impression we get of the blood is that a classification of the swarms of leukocytes seen is utterly impossible. This impression scarcely ever wears off, and the study of several hundred specimens from 27 cases of this disease leaves the writer still with the feeling that a differential count of the leukocytes with Ehrlich's triacid stain is to a considerable extent arbitrary or even impossible. Between each two of the ordinary types, there are countless transitional forms which it is impossible to classify satisfactorily under any of the recognized types. This point has been much insisted on by Weiss, and is certainly of importance. With an eosin-hematoxylin stain, which blurs several important varieties together, we find the blood less complicated ; but the simplicity comes from ignoring instead of solving the difficulties.

Myelocytes.—Nevertheless, certain essential characteristics of the blood stand out very strongly ; the most striking and important of these is the large number of "myelocytes" or nonameboid mononuclear neutrophils.

From 20 to 60 per cent. of all the leukocytes present are to be identified by their single round or oval nucleus and neutrophilic granules, as similar to the common type of marrow-cell and identical with Ehrlich's and Müller's description of "Markzellen." They are of all sizes, from 9 to 23 μ diameter, and seem at first sight to fill up almost the whole field. The nucleus is pale, usually sharply differentiated from the protoplasm, and often

¹ Müller, *Deut. Arch. f. klin. Med.*, 1., 47, 1892.

excentrically placed. Occasionally we catch one of these cells in mitotic division in the circulation, so that two distinct nuclei are seen at the poles of the cell.

Although there are nearly always from 20 to 40 per cent. of typical myelocytes (37 per cent. on the average in the writer's series), yet there are always many cells regarding which it is difficult or impossible to decide whether they are to be classed as myelocytes or not.

It will be remembered that the large lymphocyte differs from the myelocyte only in that the former has a nongranular protoplasm. Now, in leukemia of this type there are always many cells as to the protoplasm of which the conscientious observer feels in doubt. Is it granular or not? It may be diffusely stained or precisely the same violet or pink tint as the neutrophilic granules, and at certain points there are indistinct indications

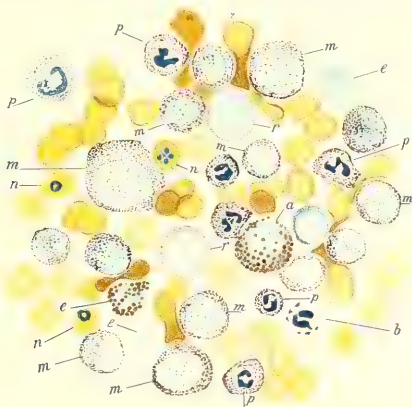


FIG. 160.—Myelogenous leukemia: *a*, eosinophilic myelocytes; *b*, "mast-cell;" *e*, *e*, ordinary eosinophile; *m*, *m*, myelocytes; *n*, *n*, normoblasts; *p*, *p*, polymuclear neutrophiles; *r*, *r*, Reizungsformen (Türk). (Cover-glass film, stained with Ehrlich's "triacid" and drawn with camera lucida.)

of granulation. Under whatever heading we class such cells, we remain dissatisfied with our judgment.

Again, the polymorphonuclear neutrophils are identical with the myelocytes, except for the shape of the nucleus; but there constantly occur in myelemia cells the nucleus of which is large and pale and excentrically placed, like that of the myelocyte, but which shows at some point an indication of a slight indentation. Shall we class such a cell as polymorphonuclear because of the single slight indentation? If we do, it seems ludicrous to lay so much stress on so small a point. If we do not, the question arises again and again as to how large an indentation a cell nucleus must possess to become "polymorphous," and the decision depends on the personal equation of the observer. We can hardly escape the conviction that there are cells in process of development from large lymphocytes into myelocytes, and from myelocytes into polymorphonuclear cells, which it is entirely impossible to classify accurately.

It is the writer's practice, in the color analysis of myelemic blood, to make

separate headings for cells intermediate between these three varieties, and give up the attempt to force all cells into any of the conventional classes.

Lymphocytes.—Cells of this type are relatively few, usually less than 6 per cent., but absolutely they are often greatly increased. The large type is more common than the small, and shows, as above noted, a tendency toward dark-purple protoplasm—darker than the nucleus, such as is not seen in normal blood, although occasionally met with in the anemias of infancy and in infectious diseases (Türk's "Reizungsformen").

Polymorphonuclear Neutrophiles.—As already mentioned, the percentage of these cells depends considerably upon the personal equation of the observer. Their small size is striking, many being under $10\ \mu$ in diameter, with intensely staining nuclei. Such forms are frequent in the normal marrow. Of the forms approximating to the myelocytic type, enough has already been said. The average percentage in the writer's cases was 49.2—*i. e.*, less than normal; but absolutely they are enormously increased, even to 70 times their normal number.

Eosinophiles.—Ehrlich's original statement regarding the presence of these cells in leukemia was that they were always *absolutely* increased. This is true, but not characteristic of the disease. Their percentage is usually about normal, occasionally somewhat increased. The striking point about them is not their excessive number, but their variations from the type seen in normal blood. Normally eosinophiles are about the size of the polymorphonuclear neutrophiles, and their nuclei are also polymorphous and very loosely connected to a mass of granules, the outline of the cell being more irregular than that of any other form of leukocyte. Now, in leukemia, one finds, to be sure, this ordinary type of eosinophile; but also much larger mononuclear eosinophiles, to which Müller and Riedel called attention under the name of "eosinophilic myelocytes." The cell is not scraggy or loosely constructed, as ordinary eosinophiles are; it is round and compact, usually larger than any normal leukocyte, and its nucleus in all ways resembles that of the ordinary (neutrophilic) myelocyte, from which it differs only by the possession of eosinophilic granules.

Dwarf forms no larger than red cells are also seen, sometimes with one nucleus, sometimes polynuclear.

Basophiles.—Almost all cases of myelocythemia show from 2 to 6 per cent. of basophiles (*i. e.*, from 3000 to 140,000 per c.mm.), usually with trilobed nucleus (though mononuclear forms are also seen), and coarse basophilic granules staining with methylene-blue or dahlia, and crowded together at the outer edge of the protoplasm. They are very irregular in size and shape, and at times one can only see light spots and streaks in a solid basophilic border. These cells are probably identical with the "mast-cells" of the alimentary canal and of connective tissue in general. Mention has been made above of the fine (*n*) granules of basophile affinity in the protoplasm of large lymphocytes; these are not to be confounded with "mast-cell" (coarse) granulations.

Irregular Forms.—Mention has already been made of the forms transitional, in appearance at any rate, between myelocytes and polymorphonuclear neutrophiles and between myelocytes and lymphocytes. Besides these, we find occasionally in leukemic blood: Nongranular polymorphonuclear cells, the protoplasm entirely unstainable or diffusely basophilic; cells of the size of the smallest lymphocytes, with neutrophilic granules; cells with two sets

of granules—*e. g.*, neutrophilic and eosinophilic, neutrophilic and basophilic, eosinophilic and basophilic—these are rare, but do occur; cells of various sizes, the peculiarity of which is in possessing not over ten granules of one or another kind, sprinkled very sparsely through their protoplasm, with wide intervals between.

Changes in the Other Tissues.—The Spleen.—The organ is tremendously enlarged and not infrequently is over a foot long, with corresponding increase of breadth and thickness, and a weight of 15 pounds is not unusual. The size of the organ in most cases gradually increases during the first two-thirds of the course of the disease, and then remains about stationary. In some cases, however, great alterations in size may occur—sudden increase from hemorrhage into the organ, sudden or slow decrease from diarrhea, intercurrent infections, or therapeutic influence. Rupture may occur spontaneously or from traumatism. The notches on the upper border—one, two, or three in number—are notable. Adhesions to neighboring organs and patches of perisplenitis are common.

The consistency is greatly increased, chiefly owing to the growth of stroma. The capsule is thickened and its surface is often coated with the results of old or recent perisplenitis in patches or diffusely, and in the stroma deposits of lime salts may occur. The section surface is, on the whole, paler and drier than normal, often mottled or marbled with brown and yellow patches on a reddish-gray background, and scarred with islands of connective tissue marking the areas of old hemorrhagic infarction. Earlier stages of the same process may be seen in other parts of the organs—red, brown, or yellow, according to the age of the lesion. The overgrowth of follicles and stroma compresses the pulp, so that fatty degeneration and atrophy result, leaving considerable quantities of pigment granules, free or enclosed in cells and surrounded by fibrous tissue. In some cases the hyperplastic Malpighian follicles stand out as grayish nodules, lobulated clusters, or beaded strings. The trabeculae are plainly seen, forming a white network across the cut surface.

Microscopically we find the increase of connective tissue very striking, except in early cases—the reticulum is thickened and often forms large scars. The Malpighian bodies are scarce. The bulk of the cells in the follicles are lymphocytes of various sizes, the small type being most numerous; but in contrast with the normal spleen, “in which the lymphocytes are the overwhelmingly predominant element,” the leukemic spleen contains remarkably few lymphocytes. Myelocytes are also numerous, though not as numerous as in the blood. Polymorphonuclear neutrophiles, eosinophiles, and mast-cells are likewise plentiful. The outlines of the follicles are usually lost in a confluence of lymphoid tissue, which sometimes accumulates into genuine lymphomas—which do not, however, consist wholly of lymphocytes, as in the lymphomas of chronic lymphemia, but contain many of the other blood and marrow elements. The number of mitoses is small. Hindenburg has observed mitosis in eosinophiles of the spleen. Myeloplaxes are also to be seen, containing debris of various kinds. Nucleated red cells are numerous and intimately mixed with the leukemic collections.

Owing to the presence of eosinophiles in the organs, Charcot-Leyden crystals can be found in the tissues, especially if the latter are left several days exposed to the air before examination. Leucin, tyrosin, xanthin, and substances allied to peptone, have been detected in the spleen by chemical analysis.

The Liver.—Considerable enlargement is present in almost every case, varying from time to time from the same causes that affect the size of the spleen. The organ may weigh 20 pounds. The enlargement is usually symmetric, but, as in other forms of enlargement, it may affect more especially the right lobe. The capsule is usually smooth or shows small patches of thickening. The consistency is increased.

The appearance of the cut surface is influenced by three elements: Stasis, fatty change (degenerative or infiltrating), and leukemic infiltration. The combinations of these processes with areas of relatively normal tissue give rise to a great variety of appearances. In general, we have a mottling of gray, yellow, and dark red, the distribution of the colors depending on the combination of pathologic processes present in the particular case.

The stasis brings about dilatation of the liver-capillaries, to which the leukemic blood brings enormous numbers of leukocytes; the centers of the acini undergo a pressure atrophy, so that the space occupied by the leukocyte-stuffed capillaries is very large.

Fatty changes in consequence of pressure or disturbed metabolism are common in advanced cases.

The true leukemic infiltration presses into the lobules from without inward, *i. e.*, from the peripheral zone toward the center. It may be diffuse or in nodular masses (lymphomas), but the origin from the periportal region can usually be made out.

Microscopically we find the leukemic infiltrations to consist of cells like those in the blood. In the dilated capillaries are large numbers of myelocytes. The lymphomas contain lymphocytes and polymorphonuclear cells with relatively few myelocytes. Eosinophiles are also very plentiful. Plasma-cells and endothelial cells are common.

The most striking and important point about the histologic changes is the enormous number of mitoses in the dilated capillaries. Nowhere else are they so numerous, not even in the germ-centers of lymphoid organs. The only other place in which Hindenburg found them so numerous was in the lymph-channels of the lymph-glands. The lymphocytes and myelocytes are the cells in which most of the mitoses occur.

Glisson's capsule is often infiltrated with lymphocytes and polynuclear neutrophiles. Large phagocytic giant cells, presumably of the leukocyte type, are numerous in the dilated capillaries; and within these cells, or outside of them, a good deal of nuclear debris and pigment is seen.

The same chemical substances mentioned in connection with the spleen have been found in the liver.

The Bone-marrow.—The fat and bone-spicules are largely atrophied, so that large pieces can be cut without previous decalcification. In place of these elements we find a great increase in the marrow-cells, both white and red. Sometimes the increase of red cells predominates, and then we get the so-called lymphoid or currant-jelly marrow; this is usually in long-standing, anemic cases. If the colorless corpuscles are especially increased, we see the "pyoid" or grayish-yellow marrow. Neither condition is at all characteristic of leukemia. Actual hemorrhages or circumscribed nodular masses are occasionally found. All the cells of the normal marrow are present in increased numbers, but the "myelocytes" (neutrophilic, with round or oval nuclei) are the most numerous, while polynuclear neutrophiles come next in frequency. The Charcot-Leyden crystals, upon which so much stress has

been laid, have been recently shown to be connected with the degeneration of eosinophiles, and can therefore be found in any tissues containing these elements after exposure to the air. They have, of course, no diagnostic value.

Lymphatic Glands.—As a rule, slight enlargement is found in all of the normal gland-chains (axillary, inguinal, bronchial, mesenteric, etc.), the enlargement being due, according to Taylor, not to lymphocytes, but to adventitious cells—myelocytes, polynuclear neutrophiles, eosinophiles, and mast-cells. These strangers compress and almost obliterate the germ-centers. Mitoses are few, and cell-degenerations frequent.

Secondary Effects of the Disease.—The pressure of the enlarged spleen and liver may give rise to ascites, enteritis, or intestinal obstruction. The spleen and liver push up the diaphragm, displacing the heart and embarrassing its action.

Metastatic Nodules.—An account of the metastases which occur rarely in this type of leukemia will be given more fully under Chronic Lymphemia, in which they are the rule. The same elements are present in the metastases which we have described in the leukemic infiltrations of the liver and spleen, namely, all the marrow-leukocytes.

Leukemic Priapism.—Various explanations of this symptom have been advanced. Pressure on the nerves or veins concerned in erection may explain certain cases. Thrombosis of the corpora cavernosa has been found in some cases, but it is doubted by some writers whether this can explain the condition.

In a case recently recorded by Kast, in which the priapism lasted till death, the corpora cavernosa were found stuffed with lymphoid tissue, while the spongy bodies consisted of tough masses of connective tissue.

Chloroma.—Occasionally and for reasons unknown, the lesions take on a greenish color, to which the name of chloroma has been applied.

Hemorrhages.—Although less diffused and less prominent than in acute cases, hemorrhages may lead to death, as by apoplexy or loss of blood in epistaxis or metrorrhagia. In a case under the writer's observation, deafness came on, due to hemorrhage into the middle ear. Hemorrhages into the spleen and marrow have been mentioned.

CHRONIC LYMPHEMIA.

Fränkel's denial (in 1895) of the existence of this condition has caused a number of observers to bring forward cases in refutation of his assertion and increased our knowledge of the disease. Cases have been recorded by Grawitz, Wertheim, Weiss, Herrick, Dock, Marischler, Hindenburg, Benda, and others. The writer has seen six typical cases. Fränkel has lately retracted his assertions.

The Blood.—**Red Corpuscles.**—In striking contrast to myelogenous leukemia, we find in chronic lymphemia an absence of nucleated red corpuscles, except in extreme cases in which the anemia has become intense. The number of corpuscles is usually reduced considerably, more than in average cases of myelogenous leukemia. Counts over 3,000,000 are seldom obtained; but in one case which the writer has followed for over three years, the red cells are always over 5,000,000. There is nothing special to be said of the finer changes of the erythrocytes, which are those already described under Secondary Anemia.

White Corpuscles.—The number may be as great as in any form of leukemia. For instance, Dock's case showed 580,000 at the time of death. One of the writer's cases had, six months ago, 1,480,000 leukocytes to the cubic millimeter; this patient is still alive. The majority of cases show, however, lower counts than the average in myelogenous cases. The other cases of the writer had from 80,000 to 25,000, and this is about what we expect to find. One subacute case had, six weeks before death, 132,000 leukocytes per cubic millimeter.

Color analysis shows that practically all the white corpuscles present are of the small lymphocyte type—over 99 per cent. in Dock's case, 99.9 per cent. in one of the writer's, 98.6 per cent. in another. These lymphocytes correspond in all respects to those of normal blood; that is, they may have light or dark nuclei, visible or invisible protoplasm; their nucleus is generally round, occasionally indented, rarely double. The small remnant of leukocytes other than lymphocytes may be made up of any of the other varieties—*i. e.*, of eosinophiles, myelocytes, or polynuclear neutrophils. Thus, in Dock's case the eosinophiles were about 1 to every 2000 lymphocytes; the myelocytes 1:5000. In one of the writer's cases, there was at first 1 polymorphonuclear neutrophile for every 1000 lymphocytes, with no other varieties at all. Later, eosinophiles and myelocytes in very small numbers became visible. The excess of lymphocytes is not always so extreme, however. Another of the writer's cases showed, among the 80,000 leukocytes per c.mm., the following: Polymorphonuclear neutrophils, 17.2 per cent.; small lymphocytes, 80.5 per cent.; large lymphocytes, 2.1 per cent.; eosinophiles, 0 per cent.; myelocytes, 0.2 per cent.

The contrast of chronic lymphemia and chronic myelocythemia is as sharp as possible: in the first, an endless monotonous expanse of lymphocytes, all pretty much alike; in the second, every possible type of leukocyte, granular and nongranular.

Changes in the Blood-making Organs.—**The Spleen.**—As a rule, the enlargement is moderate; the organ projects one or two fingers' breadth below the costal margin, and is perhaps seven to nine inches in length. But occasionally the enlargement is as great as in any form of leukemia. In Dock's case the organ reached from the eighth rib in the axillary line to the left iliac fossa and across to the middle of the left rectus muscle. In a case which the writer has recently seen, the spleen was even larger, extending decidedly to the right of the navel. In view of these facts, it is entirely improper to speak of "splenomyelogenous" leukemia, since both spleen and marrow (see page 490) may be equally affected in lymphemia.

The other characteristics of the spleen (as regards density, color, etc.) are the same as those already described in the myelogenous form of the disease. The greatest difference is, however, seen when we come to the microscopic appearances.

Microscopic Appearances.—The bulk of the cellular constituents, like those of the blood, is made up of small lymphocytes; whereas in acute lymphemia the prevailing type of cell is that commonly seen at the germinal centers of lymphoid follicles, and the surrounding zone of small dark daughter-cells is much reduced or gone, in chronic lymphemia the small dark lymphocytes have everything their own way, and the larger and paler mother-lymphocytes are much less in evidence. In the spleen we may have

a diffuse increase in the number of the normal follicles or definite lymphomas forming solid grayish nodules made up almost entirely of lymphocytes. As in the acute lymphemias, the distinction of germ-center and boundary zone is wiped out.

The Liver.—As a rule, the organ is not greatly enlarged; but now and then it reaches to the navel. The leukemic process in it is usually confined to metastatic lymphomas, which stand out strikingly as grayish nodules on the dark-red section-surface and may be seen beneath the capsule. Occasionally we find diffuse infiltration of the whole liver-substance, with numberless mitoses in the capillaries, with or without circumscribed lymphomas.

Lymphatic Glands.—Any or all of the visible lymphatic glands may be enlarged. Masses in the neck, axillary, and groins are notable, but seldom attain the size seen in Hodgkin's disease. The mesenteric, retroperitoneal, and bronchial glands, the lymphoid tissue of the mouth, throat, and gastro-enteric tract, are often affected. The structure of these glands is that already described in the case of the spleen; masses of small lymphocytes make up the whole of it.

Metastatic Nodules.—The number of metastatic lymphomas is greater and the distribution more widespread than in any other form of leukemia. The serous membranes (pleura, peritoneum, pericardium, etc.), all the mucous membranes, the skin, the organs of special sense, the brain and meninges, the heart, lungs, kidneys, pancreas, and sexual organs may any or all of them be affected. The metastases appear as grayish, circumscribed nodules, not different in appearance from metastatic sarcomas; but microscopically they are made up wholly of masses of small lymphocytes, arranged as in the organs before described. Metastases in the bone-marrow often occur, and the marrow is almost always hypertrophied, and evidently takes an important part in the process; but the hypertrophy is not of the normal marrow-elements, which are crowded out and almost abolished by the lymphocytic infiltration. The usual marrow-elements (eosinophiles, nucleated red cells, neutrophiles, and basophiles) are therefore greatly diminished in the marrow, as well as in the blood.

ACUTE LYMPHEMIA.

Etiology.—Most cases occur between the ages of eleven and twenty-four. Males slightly predominate. Many points about the disease suggest an acute infection, and it has been maintained that the lesions so frequently found in various parts of the alimentary tract might give entrance to micro-organisms. Abrastov reports two cases which strongly suggest contagion. But no positive evidence on these points has yet been presented.

The Blood.—The blood of truly acute cases—that is, of cases where the acute symptoms and speedy course to death within a few weeks is not simply the end-stage of a chronic leukemia—is usually of a definitely different type from that of other varieties of leukemia. It is almost always a lymphemia; for, while not all lymphemias are acute, almost all acute cases are lymphemic—that is, the blood-leukocytes correspond rather to those found normally in the lymphadenoid apparatus than to those predominating in the marrow. But the blood shows in the great majority of cases a different state of things from that already described under Chronic Lymphemia. We will begin with the point of greatest interest, namely, the leukocytes.

Leukocytes.—As a rule, the total count of leukocytes is smaller than

that of any other form of leukemia. From 30,000 to 70,000 per c.cm. is the ordinary count. As in other forms of leukemia, the number varies greatly from time to time, and is usually much decreased during the course of any intercurrent infection (sepsis, pneumonia, etc.). It may possibly be affected by treatment, but this is more than doubtful.

The following table illustrates the effect of an intercurrent septicemia on the count, in a case watched by the writer. The diminution of the number was associated with a great increase of degenerating forms in the blood.

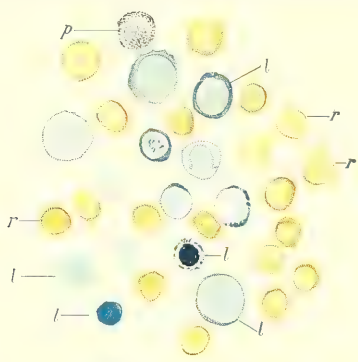


FIG. 161.—Lymphatic leukemia : *l*, *l*, *l*, lymphocytes ; *p*, polynuclear neutrophile ; *r*, *r*, red cells.

Date.	Leukocytes per c.mm.	Percentage of lymphocytes (large and small).
April 3	31,600	96.5 per cent.
" 4	31,000	
" 6	28,505	93.6 per cent.
" 8	44,000	
" 10	31,000	95.5 per cent.
" 12	40,000	
" 13	Sepsis began.	
" 20	5,661	
" 21	4,000	
" 22	3,400	92.0 per cent.
" 24	3,200	
" 28	800	
" 29	471 !	94.7 per cent.
Death on 29th.		

As indicated in this table, the percentage of lymphocytes is very high, not markedly different from that of chronic lymphemia. It remains so, as a rule, despite the influence of the intercurrent affection on the total count ; in other words, this intercurrent complication does not change the method in which the cells are produced. But, though the percentages remain the same, there is a change in the appearance of the cells, which probably explains the diminution in the total count. This change consists in the increase of degenerative forms, until sometimes hardly a sound leukocyte is to be seen. This leads us to suppose that a wholesale cell-destruction is taking place under the influence of the complicating infection. The supposition is

strengthened by the fact that the spleen and lymph-glands grow smaller and softer at the same time and show microscopically evidence of extensive cell-destruction; the simultaneous increase in the uric acid excreted in the urine is another evidence of cell-destruction.

But although the percentage of lymphocytes is about the same as in chronic cases, we find that the increase of lymphocytes is made up chiefly of large and medium-sized pale forms, and not exclusively of the small dark forms characteristic of chronic lymphemia. The subacute cases show a preponderance of a type of lymphocyte intermediate between the smallest and the largest. In general, although no line can be drawn between chronic, subacute, and acute cases, we can say that, as a rule, the more acute the case, the larger the lymphocytes.

The large lymphocytes of acute leukemia correspond exactly in many instances with those of normal blood. The great majority contain a large nucleus, with but faint affinity for coloring matters of any kind. This nucleus is often indented or even double. What is more peculiar to this disease is the relatively large number of lymphocytes showing evidence of division; in some instances, such cells are very common. Another feature is the frequency of signs of degeneration in the large lymphocytes. Even in normal blood, this form of leukocyte is especially apt to show degenerative changes; but in some cases of acute leukemia these changes are seen in almost every cell. All forms of leukocytolysis, according to the elaborate researches of Botkin,¹ can be studied in acute leukemia, especially when some intercurrent infection takes place.

(a) The whole leukocyte may swell symmetrically, the nucleus becoming vacuolated and fading indistinguishably into the surrounding protoplasm, which stains more intensely than the nucleus.

(b) The nucleus may remain relatively unaffected in size and staining reaction, while the protoplasm disappears altogether or is seen only in tattered fragments around the nucleus.

(c) The whole cell may swell as in the first type (a), the protoplasm being unstained except at its outer rim.

Combinations of these types are also to be seen; Litten has noticed fatty degeneration of the leukocytes.

As mentioned above, the lymphocytes of acute leukemia may show two nuclei; but they do not remind us at all of the polymorphonuclear neutrophils, (a) because they never contain neutrophilic granules, (b) because their nuclei are well separated, pale, and round or oval, never twisted or fragmented, like true polymorphous nuclei, (c) because of the frequent presence of fine basophilic granulations in their protoplasm.

The dividing or divided forms are much less common in the peripheral capillaries than in those of the internal organs (*e. g.*, lungs, liver, kidneys), where they are very abundant (Fränkel). All that is needed to make the leukocytes divide in this disease is a slowing of the circulation. The special conditions of the blood-making organs are helpful, but not essential.

Fränkel saw no ameboid movements whatever in these lymphocytes, and this is also the writer's experience.

As stated above, all other varieties of leukocytes—polymorphonuclear neutrophils, eosinophils, and myelocytes—generally disappear from the blood, but occasionally a few of each of these varieties are seen.

¹ *Virchow's Archiv*, cxlv., 1896.

Red Corpuscles.—The red cells are usually much more reduced than in chronic cases, not infrequently falling nearly to one million before death. The usual deformities of severe anemia are seen. Regarding nucleated red corpuscles, the blood stands midway between that of chronic myelogenous leukemia, in which the number of erythroblasts is very great, and chronic lymphemia (chronic lymphatic leukemia), in which they are very scanty or altogether absent. The number approaches that seen in severe secondary anemia—which is, in fact, present in this form of the disease. Normoblasts form the great majority of the erythroblasts found, but megaloblasts also appear occasionally. Cases occurring in children form an exception to this rule; in them, nucleated red cells are usually very abundant, as is the case in nearly all severe diseases affecting the blood of infants.

Fränkel noticed an enormous accumulation of uric acid in the blood, 22 mgr. in 100 c.c.

Postmortem Appearances.—The color of the blood is rarely noteworthy in acute cases, unless extensive coagulation has taken place; that is, in autopsies performed immediately after death, the color of the blood is not usually such as to attract attention. The most striking feature macroscopically is the presence of countless hemorrhages in the skin, in all mucous and serous surfaces, and in the organs themselves. Hemorrhages may occur in the brain or subdural space. In the internal ear, the mouth, gums, esophagus, larynx, stomach, intestine, pleura, peritoneum, bladder, vagina—in all the internal organs, the pelvis of the kidney, and in numberless other situations—hemorrhages of varying amount may be seen. They are useful as guides; for wherever we find hemorrhages, we are sure to find lymphomas, either macroscopic or microscopic.

The alterations of the lymphadenoid apparatus divide themselves as follows: (a) Those in the normally visible lymph-glands, including those of the whole gastro-enteric tract; (b) those in the spleen and bone-marrow; (c) metastatic lymphomas.

Visible Lymph-glands.—The adenoid tissue is transformed into soft whitish or grayish-red tumors, the cut surface of which is sprinkled with spots of hemorrhage. The glands are not greatly enlarged, compared with those seen in chronic lymphemia or in Hodgkin's disease; for they are seldom larger than a walnut, and usually smaller. "The characteristic point about them is their thoroughly atypical, nonregional distribution" (Benda). One meets, for example, with a combination of axillary and mesenteric enlargement, such as is seen in no other acute disease, unless it be secondary syphilis. Occasionally the disease may be confined to the alimentary canal and bone-marrow; the spleen, axillary, inguinal, mesenteric, and bronchial glands remaining normal.

Spleen and Bone-marrow.—The spleen is nearly always symmetrically enlarged, although not nearly to the extent seen in chronic lymphemia or chronic myelogenous leukemia. One rarely sees a spleen over eight inches long, with corresponding thickness and breadth. It is usually softer than normal, contrasting in this respect with the firm, tough spleen of chronic cases. There is a lack of distinction between pulp and follicles. An elastic but not fluid mass projects between the trabeculae and vessels. The section surface is of a uniform grayish-red color.

The bone-marrow always shows some alterations, but their extent varies greatly in individual instances. We may have (a) spots of red lymphoid

marrow, or hemorrhages into the marrow; (b) large tracts of red marrow, as, *e. g.*, one-half the femur or more; (c) homogeneous, grayish-red or "pyoid" marrow, with here and there yellow-greenish portions; (d) discrete, pale, grayish-white nodules scattered here and there (these are much more common in chronic cases).

"In a general way, the gross appearances of the marrow stand midway between those of pernicious anemia and those of chronic leukemia, but approximate more nearly to the first" (Benda).

Metastatic lymphomas are always numerous, far more so microscopically than the gross appearances suggest. In acute cases they are usually very small, and are visible to the naked eye only when aggregated in large numbers or confluent. As has been stated, they are to be found wherever we find hemorrhages. But many light areas, which macroscopically appear to be lymphomas, turn out to be something else: *e. g.*, in the liver, fatty changes; in the kidney, embolic abscesses. These conditions may exist side by side with genuine lymphomas.

There is no organ in which the lymphomas may not be found. Benda mentions the following list: The myocardium, pericardium and endocardium, the pleura (extending in one case to the lung), liver, kidney, renal pelvis, ureter, and prostate, in the meninges, brain, pons, and infiltrating the cerebral nerves. The ulcerations of the mouth and gums, which form so prominent a clinical feature, are usually dependent on lymphomatous metastases there. The larynx is also often involved, at times to such an extent that symptoms of suffocation, necessitating tracheotomy, appear.

In Askanazy's case, the whole alimentary tract was studded with accumulations of lymphoid tissue, the solitary follicles and Peyer's patches being everywhere enlarged and partly ulcerating, and the stomach showing erosions and hemorrhages due to lymphoid infiltration and pressure necrosis.

In a recent case of Fränkel's, the facial nerve was infiltrated with lymphocytes, which extended between the fibers of the nerve itself. Similar changes were found in the acoustic nerve and in the vagus. During life these lesions caused facial paralysis, deafness, and palpitation. The writer has seen an eyelid infiltrated and greatly thickened by similar growths, and the eye pushed forward by a growth in its rear.

Large-sized lymphomas, such as are common in chronic lymphemia, do not usually form in acute cases, perhaps for lack of time.

Microscopic Appearances.—In many cases the same elements occur in all the lesions, no matter in what organ or on what surface they are planted. Occasionally there is a difference between the marrow changes on the one hand, and those of the gland-tumors and metastatic nodes on the other.

The greater part of the gland-tumors is made up of cells corresponding exactly to those previously described as "large lymphocytes" (Ehrlich's large mononuclear elements, Löwit's "Leukoblasts," Müller's "Theilungs-reife Zellen," Benda's "Lymphogonien"); that is, they are cells of about 12 μ diameter, containing a pale-staining, finely reticulated nucleus, usually round or kidney-shaped, and surrounded by a varying amount of protoplasm, which is either free from granules or contains very fine, closely packed basophilic granules, and which itself has a faint affinity both for acid and basic stains, or remains entirely unstained. In the normal lymph-

gland these cells divide to form the ordinary small lymphocytes of the blood and lymph, this division taking place in the "germ-centers," around which the "daughter-cells" (small lymphocytes) are arranged in large numbers, so that they appear to make up most of the gland substance.

In acute lymphemia, it is still these cells in which most of the mitoses are found; but germ-centers there are none. All distinction of germ-centers and sinuses is lost, and only the large central sinus and the lymph-vessels leading from it can be made out. There is seen a small number of small lymphocytes scattered singly or in clumps among the large lymphocytes; but in these small forms the number of mitoses is relatively slight, and the total effect of the section is that the small cells have been largely replaced by large ones.

The spleen and metastatic nodules show similar appearances, but in the spleen the excess of large over small lymphocytes is less striking than in the lymph-glands, and hemorrhages are more abundant. There is good reason to suppose that metastases are due to a "colonizing" activity on the part of the cells of the circulating blood.

When metastases occur in the mucous membrane of the alimentary canal, we find in the deeper layers the usual abundance of "mastzellen," and in the superficial layers near the surface polynuclear cells. This corresponds to the normal arrangement of the leukocytes of the alimentary canal, on which the cell system of the metastatic lymphomas is grafted.

Microscopically the marrow shows, of course, the same wide variations in individual cases that have been alluded to in its gross appearances. In the cases showing macroscopically nothing but a greater or less amount of red marrow instead of fatty marrow, the microscope shows principally nucleated red cells mixed with eosinophiles and small myelocytes. In the more pyoid cases there are found chiefly large mononuclear cells exactly like those in the lymph-glands, but possessing, many of them, neutrophilic or basophilic granulations. In such cases eosinophiles, erythroblasts, and polymorphonuclear cells are rare. The main type of cell is, even in the marrow, the lymphocyte.

In the lungs Taylor found the infiltrations around the branches of the pulmonary vessels, around the bronchi and alveoli, and beneath the pleura—*i. e.* in the situations where lymph-nodes are normally found. In the bronchi no lymphocytes were seen.

The changes present in acute leukemia, then, amount only to an intensely vigorous growth of the normal cells of the whole lymphadenoid apparatus and bone-marrow, and are thereby distinctly different from chronic lymphemia, which consists wholly of a heaping-up of small lymphocytes in neoplastic form; different also from chronic myelogenous leukemia, where the marrow elements are those chiefly affected. Yet the glandular tumors of acute leukemia are not entirely unlike those of chronic lymphemia, and the marrow changes may resemble those of chronic myelogenous leukemia. So far, no one has reported any metastatic myelomas, or tumors containing indubitable marrow elements (such as are seen in myelogenous leukemia), in the truly acute cases.

Sections through blood-clot can hardly be distinguished from those through the enlarged glands, showing the apparently complete identity of the cells in the blood with those of the organs; and further, examples of every variety of cells found in the organs occur in the blood. However,

a larger proportion of the large lymphocytes in the bone-marrow show neutrophile granules (myelocytes) than in the blood.

The absence or great diminution of polymorphonuclear neutrophiles in the blood is matched by their great diminution in those limited portions of the blood-making organs in which they are chiefly found under normal conditions—viz., in the marrow-veins and in the lymph-sinuses.

As in other varieties of leukemia, the succession of events is probably this : (1) Action of an unknown stimulus on the blood-making organs ; (2) proliferation of leukocytes in the blood-organs (continued to a greater or less extent in the blood) ; (3) the discharge of these leukocytes into the blood before their normal metamorphosis is finished ; (4) "colonization" of these blood-leukocytes as metastatic nodules.

Where abscesses occur, as in the kidney (*vide supra*), we find them filled, as usual, with polymorphonuclear neutrophiles. This is hard to explain on the usual theory of emigration from the blood, since the blood in such cases contains hardly any neutrophiles. Benda supposes that the lymphocytes of the neighboring metastatic nodules are transformed *in situ* into polymorphonuclear cells—a supposition which seems to the writer very unlikely.

It has been observed by various authors that the effect of an intercurrent infection (septic or other) is not simply to diminish the number of leukocytes (*vide supra*), but often to cause a considerable shrinkage of the tumefied organs, similar to the retrograde changes in sarcomas under the influence of a complicating erysipelas. This is apparently due to cell death, as there is every evidence of cell destruction in the blood and organs of such cases, and the uric acid becomes enormously increased in the urine—an indication that great numbers of nuclei have perished.

In some chronic myelogenous cases there is, as above stated (page 488), an increase and not a diminution of the leukocyte-count, under the influence of infectious complications ; but in acute leukemias this is apparently not the case.¹

Summary.—Leukemia appears under three principal types : Chronic myelocythemia, chronic lymphemia, acute lymphemia.

The first type is characterized by a very large spleen and liver, in which, as well as in the blood and marrow, the marrow types of cells are found. Stages of leukocyte structure intermediate between those seen in normal blood are here present in the blood and organs, giving a very "polymorphous" appearance to them. The characteristic marrow-cell, or mononuclear neutrophile, forms nearly one-half the cellular elements in the blood and organs. The lymphatic tissue, outside of the spleen and marrow, is but little affected.

In chronic lymphemia the blood and organs are flooded with small lymphocytes, the other types of leukocytes being so far reduced as to be hardly noticeable. Large metastatic lymphomas are scattered through the whole organism. The spleen and marrow may be as much affected as in myelocythemia ; but the type of cell found prevailing is entirely different, and the peculiar marrow elements are replaced by small-cell lymphoid tissue.

In acute lymphemia, hemorrhages and ulcerations are prominent. The blood and the blood-making tissues contain great numbers of large pale lymphocytes, like those of the germ-centers of normal lymphoid tissue. Metastatic lymphomas are very numerous, but are generally mostly microscopic in size. No marrow elements are found in the blood or organs,

¹ Except at the time of death.

although in the marrow itself they are less decreased than in chronic lymphemia. The blood-vessels themselves are invaded and ruptured by leukemic infiltration; hence the acuteness of the disease and the frequent hemorrhages.

HODGKIN'S DISEASE.

There is little to be said of this disease which has not already been said of leukemia. Our ignorance of its etiology is of the same degree, its pathology is identical with that of chronic leukemia, and its blood condition is wonderful only in being so entirely normal.

Two points especially deserve discussion: (*a*) Is it a separate disease at all? (*b*) Why is the blood normal (the organ changes being identical with those of leukemia)?

There is little doubt that many cases considered as Hodgkin's disease have been in reality cases of tuberculous or syphilitic adenitis. Only the most careful study can at times distinguish these diseases from Hodgkin's disease. The diagnosis can therefore never be made with certainty during life, and it has been asserted by various writers that what we call Hodgkin's disease is really a congeries of cases, some tuberculous, some syphilitic, some malignant disease, some early leukemia, and some chronic malaria. The distinction between the disease and the various forms of sarcoma of the lymph-glands cannot be made either during life or by the microscope, as there are no reliable differences in cell structure. This haziness is mirrored in the various names given to the affection: Lymphadenoma, lymphosarcoma, lymphoma, malignant lymphoma, pseudoleukemia, splenic anemia, etc.

If the disease is simply an hypertrophy of adenoid tissue without known cause, we cannot well limit the name to the hypertrophy of any one set of adenoid organs, and must admit pure splenic or myelogenous types, as has been done by most German authorities. But this leads to difficulties and even absurdities.

Where a large number of glands is affected, where the course is slow and creeping, and tuberculosis and syphilis can be excluded with reasonable certainty, the diagnosis of Hodgkin's disease seems a natural one. But when only a few glands, only the spleen, or only the marrow is found hypertrophied, we may well feel that the name is little more than a cloak for our ignorance.

Many French writers insist on regarding it as a preleukemic stage of leukemia, basing their theory on a few cases recorded many years ago, in which a transition to true leukemia is said to have occurred. The writer has never been satisfied with the evidence that such cases exist; at any rate, they must be exceedingly rare. It is more likely that the leukocytosis which often appears in the later stages of the disease was mistaken for leukemia, owing to the absence of accurate methods of blood examination.

On the whole, we must regard the question of the nature of the disease and its relations to sarcoma as wholly unsettled, but there is no reason for supposing that it has any close relationship to syphilis or tuberculosis. The existence of pure myelogenous cases is not yet satisfactorily established. Splenic enlargement without symptoms should not, the writer believes, be classed as Hodgkin's disease.

On the question of the relationship of the disease to leukemia, the researches of Benda have recently thrown some light. In leukemia, something occurs which sets free in the blood-current the masses of leukocytes,

produced in the organs equally in leukemia and in Hodgkin's disease. What is this "something"?

Troje assumes a riddling of the septa which normally divide the germ-centers from the lymph-channels, and of the marrow-veins. Benda adds to this hypothesis the fact that he has observed, in leukemic cases, extensive changes in the vessels. Both in the primary growths and in the metastatic nodules he finds the vessel-walls invaded with lymphoid tissue, so that the leukocytes can easily burst through into the vessels. Frequently the elastic layer and the intima up to the very endothelium are riddled with lymphoid growths, and in the larger veins he finds lymphomas projecting into the lumen of the vessel and covered only by endothelium. In Taylor's cases the endothelium was ruptured. The protection afforded to the organism by thrombosis, when, in diseases like tuberculosis, carcinoma, or syphilis, the vessels are invaded, is wanting in leukemia. For some reason, vessels invaded by lymphomas do not become the seat of thrombosis, perhaps because the cells of the lymphoma are such near relatives of those of the blood and excite no reactive hostility, while the products of tuberculosis or cancer, being more foreign to the blood, induce thrombosis.

Benda's observations do not, of course, explain why the lymphomas of Hodgkin's disease do not invade the vessels; but, according to him, they do not do so.

The Blood.—As a rule, there are no changes in the blood, except a progressive anemia of the secondary type, seen chiefly toward the close of the disease and often accompanied by more or less polymorphonuclear leukocytosis. Sometimes this is obviously dependent on suppurations in the enlarged glands; in other cases, its origin is not clear. During the greater part of the course of most cases, the leukocyte-count is normal, with often a slight lymphocytosis.

Lymphadenoid Organs.—The cervical glands are those earliest involved; later, the intrathoracic, axillary, inguinal, and mesenteric glands. The growths in the neck may be as large as a child's head. They are soft, movable, and discrete in the earlier stages, becoming harder and more matted to each other and to the skin in the later stages. Usually the disease remains limited by the capsule of the glands, but it may pierce through and proliferate outside of it. Softening and suppuration occur but rarely.

The spleen may be as large as in any form of leukemia; but, as a rule, it is not so, being only slightly larger than normal, and containing perhaps circumscribed lymphomas. The disease corresponds rather to chronic lymphemia than to the other types of leukemia, in respect of the changes in the organs; that is, we usually find circumscribed lymphomas as metastases, rather than diffuse infiltration such as would produce great enlargement of organs, like the spleen and liver. The distribution of metastases may be as wide as in lymphemia, and there is no organ or surface—serous, mucous, or epidermal—that may not be invaded. Gastro-intestinal forms of the disease have been described.

Microscopically we find in all advanced cases, first, a great increase of stroma in the lymphadenoid organs, then the hyperplasia of lymphoid cells, as described in leukemia. Goldmann noted the presence of a zone of eosinophiles outside of the boundary zone of small lymphocytes in the follicles. The writer has not seen any account of marrow elements in the lymphomas or metastases, most observers not taking the pains to decide this point.

THE CIRCULATORY SYSTEM.

THE ORGANS OF CIRCULATION.

THE HEART.

Congenital Abnormities.—Malpositions of the Heart.—The most serious form of malposition of the heart is *ectopia cordis*, a condition in which the organ is situated outside of the thorax. In *ectopia cordis pectoralis*, the sternum is divided longitudinally by a median fissure, in which case the heart is entirely exposed or covered merely by the integument; in grave cases life is of short duration. In *ectopia cordis abdominalis*, the organ is situated below the diaphragm; it may be found between the stomach and abdominal wall, in the neighborhood of one of the kidneys, or with other viscera in an umbilical hernia. Patients with this anomaly may live for years; Peacock reports a case in a man forty-seven years of age. In *ectopia cordis cervicalis*, the heart is in the neck, under the ramus of the jaw. In this condition, extra-uterine life is short.

There are other misplacements of the heart, of a less serious nature; thus, it may occupy a median position, as in the fetus, or it may lie transversely. Again, the organ may lie on the right side of the body (*dextrocardia*), in which case there is usually a similar transposition of the abdominal viscera (*situs viscerum inversus*).

Abnormities in Size.—As Rokitansky, Virchow, and others have pointed out, hypoplasia of the heart and arteries is sometimes found in association with chlorosis; it is also a usual accompaniment of the lymphatic constitution—*i. e.*, a condition in which there is hyperplasia of the lymphoid tissues and persistence of the thymus gland. Congenital hypertrophy of the heart is usually a sequence of fetal endocarditis, or is an accompaniment of some malformation, such as septal defect or stenosis of one of the large vessels. Very rarely no other abnormality is present to account for the hypertrophy; and under these circumstances the condition is to be regarded, according to Virchow, as an example of a diffuse myomatous neoplasia.

Defects and Diverticula of the Pericardium.—Deficiency of the pericardium may be complete or partial; it is usually associated with other vices of development, particularly with *ectopia*. Congenital diverticula are rare; they consist in a protrusion of the serous layer through the fibrous portion, which is unnaturally thinned.

Defects of the Auricular Septum.—Complete absence of the auricular septum is a rare deformity, and makes the heart a trilocular organ; or, in case the ventricular septum is also wanting, a bilocular organ. More commonly the septum is only in part deficient, and in these cases the foramen ovale may be closed or patent.

Patent Foramen Ovale.—This is one of the most common defects. It may exist alone; in which case, no serious disturbances may follow.

Generally, however, there are other abnormalities, such as stenosis of the pulmonary artery or a defect in the ventricular septum. In some instances delicate cords, resembling the chordæ tendineæ, are stretched across the open foramen.

Defects of the Ventricular Septum.—This deficiency may be complete or partial, more commonly the latter. Very often there is a single round or oval opening in the pars membranacea or “undefended space.” In other instances the two ventricles communicate through several openings. Defects of the ventricular septum are usually associated with a patulous state of the foramen ovale and abnormalities of the large vascular trunks, such as stenosis of the aorta or pulmonary artery, or transposition of these vessels.

Stenosis and Atresia of the Pulmonary Artery.—Constriction of the pulmonary artery may be complete or partial; the former is rare, while the latter is common. The narrowing may involve the trunk of the vessel, the conus arteriosus, or the orifice. Stenosis, especially when it involves the orifice or the conus, is often the sequence of a prenatal inflammation. Atresia, on the other hand, is probably the result of an abnormal division of the truncus arteriosus. In many cases the ventricular septum is deflected considerably to the left, sometimes to such a degree that the aorta springs from the right ventricle. The latter is often much enlarged, not only at the expense of the left ventricle, which is unduly small, but also from an actual hypertrophy, the result of the extra demands made upon the right ventricle. When, however, the atresia develops after the closure of the ventricular septum (third month), it gives rise to hypertrophy of the left ventricle, as the latter in such a case must carry on both the systemic and the pulmonary circulations. Constriction of the pulmonary artery is usually associated with a patulous foramen ovale or an incomplete ventricular septum and a pervious ductus arteriosus, through which the blood is carried to the lungs.

Stenosis and Atresia of the Aorta.—All degrees of constriction of the aorta are observed, from slight narrowing to complete obliteration. The stenosis may involve the left conus, the orifice, or the arch near the ductus arteriosus. Waldstein has collected 113 cases of narrowing and closure of the aorta at or near the ductus arteriosus. In marked stenosis or atresia of the orifice, the ventricular septum being closed, the ductus arteriosus and the foramen ovale usually remain open, so that the right ventricle carries on both the systemic and pulmonary circulations through the pulmonary artery. In constriction of the arch between the ductus arteriosus and the left subclavian, the collateral circulation is effected by means of anastomosis between the branches of the subclavian and the descending aorta.

Transposition and Malposition of the Large Blood-vessels.—Occasionally the pulmonary artery is derived from the left ventricle, and the aorta from the right ventricle. More frequently, from a deviation of the septum to one side or the other, the two vessels have their origin in the same ventricle. These abnormalities are usually associated with a patent foramen ovale and a pervious ductus arteriosus. Sometimes the septa are also defective.

Persistent Ductus Arteriosus.—A pervious ductus arteriosus is a common accompaniment of septal defects and stenosis or atresia of the large vessels. When it exists as the sole lesion, it is not incompatible with long life. Sometimes the perviousness is only partial; in some instances the duct has been found aneurysmatically dilated.

Malformation and Defects of the Valves.—The most common valvular anomalies are those which affect the number and size of the segments. Union of the segments is occasionally encountered at the auriculoventricular valves, and may be the result of a malformation or a fetal endocarditis. There may be two or four semilunar valves, instead of three; the presence of two is usually due to an ancient endocarditis that has altered two of the leaflets in such a way that they form one large pocket.

THE PERICARDIUM.

Hydropericardium.—Hydropericardium, or dropsy of the pericardium, consists in an antemortem accumulation of serous fluid in the pericardial sac, independent of any inflammatory changes. As a rule, a small quantity of clear fluid is found postmortem in the pericardial sac, irrespective of the cause of death. This transudation is devoid of pathologic significance; it takes place naturally during the agonic period or shortly after death, and usually amounts to from 10 to 20 c.cm., or occasionally even to 100 c.cm. When the accumulation is in excess of these quantities, it has probably been formed antemortem; and under such circumstances, it is regarded as true dropsy.

The causes of hydropericardium are such as give rise to serous infiltration in other parts of the body; thus, Bright's disease and chronic heart disease are the most important factors. It is sometimes dependent upon a grave anemia or some general condition affecting the blood, such as tuberculosis, cancer, or scurvy. Aortic aneurysms, mediastinal tumors, chronic pulmonary affections, and chronic mediastinitis occasionally lead to stasis in the pericardial veins and to serous exudation into the pericardium.

The amount of fluid varies from a few ounces to a pint or more. It is usually clear and of a pale yellow or greenish hue. Slight turbidity may be occasioned by the presence in large numbers of desquamated endothelial cells. In rare instances the fluid is milky from admixture with chyle (chylopericardium). In cachectic states the effusion may be red from the presence of blood; and in jaundice it is dark yellow from the presence of bile. Degeneration of the surface endothelium and maceration of the pericardium may result from prolonged contact with the fluid.

Hemopericardium.—The accumulation of blood in the pericardium, independent of inflammation, may result from wounds of the heart; from spontaneous rupture of the heart; from rupture of aneurysms of the aorta, pulmonary artery, or coronary arteries; or more rarely from some general disturbance which affects seriously the blood-crisis, such as scurvy, purpura, or leukemia.

Under certain conditions the effusion in pericarditis may be mixed with more or less blood. This is commonly the case when the inflammation is dependent upon tubercle or cancer, or is associated with some grave cachexia.

The quantity of blood extravasated varies from a few ounces to several pints. Large accumulations are usually associated with small openings, since the movements of the heart are not arrested so quickly when the distention of the sac is gradual as when it is sudden.

The appearance of the blood is variable; it may be fluid or partly clotted. Not infrequently, when the condition does not prove immediately

fatal, inflammatory changes are excited in the pericardium by the presence of the blood.

Pneumopericardium.—Pneumopericardium, or the accumulation of gas in the pericardium, is an extremely rare affection. As in nearly every instance the air is associated with a certain amount of fluid, generally serum or pus, the condition is more correctly termed hydropneumopericardium or pyopneumopericardium. About one-half of the recorded cases have resulted from traumatism, the pericardium having been torn by a penetrating wound of the chest, a fractured rib, or a foreign body impacted in the esophagus.

The next most frequent cause has been the entrance of air through extension to the pericardium of some ulcerative process in a neighboring air-containing organ; thus it has been produced by a pneumopyothorax, or a phthisic cavity in the lung, an ulcer in the esophagus, or a gastric ulcer or cancer.

Cases are now and then encountered which have resulted from the decomposition of a purulent effusion by gas-producing bacteria.

Acute Pericarditis.—**Etiology.**—Excepting the rare cases in which inflammation follows some direct injury, pericarditis may be regarded as a secondary process. Rheumatism is by far the most frequent cause of the disease; of 100 cases analyzed by Sears, 51 were directly associated with acute rheumatism. While pericarditis may develop in the mildest type of rheumatism, there is greater liability to it when several joints are affected and the constitutional symptoms are severe. It is not an uncommon complication in various septic processes and specific fevers, such as septicemia, pyemia, gonorrhea, scarlet fever, chorea, and small-pox. Constitutional diseases, like gout, diabetes, and scurvy, are occasional antecedents. Involvement of the pericardium by extension of disease from adjacent structures is of frequent occurrence. Thus, pneumonia or pleurisy, especially when on the left side, may be followed by pericarditis. Pneumonia was the cause in 18 of Sears's cases. Osler found pericarditis in 5 of 100 fatal cases of pneumonia; in 4 of these the lappet of the lung overlying the heart was solidified. In some instances the inflammation results from the extension of acute myocarditis or endocarditis, but when these diseases are associated it by no means follows that the pericarditis is secondary; it may be primary, or, as is doubtless often the case, it may have developed independently from the action of the same morbid agents that caused the other cardiac lesions. Now and then pericarditis is secondary to such affections of neighboring parts as caries of the ribs or sternum, suppurating lymph-glands, mammary abscess, or ulceration of the esophagus. In these conditions, invasion of the pericardium may be effected through an actual rupture of the serous membrane, though this is exceptional. As the pericardium covers a large part of the ascending portion of the arch of the aorta, aneurysm in this locality may set up adhesive inflammation. Several cases are recorded in which an acute attack of pericarditis developed after occlusion of the coronary arteries by an embolus or thrombus. Finally, the primary focus of irritation may be located below the diaphragm; thus, an ulcer of the stomach may not only cause adhesion of the pericardial membranes, but may actually rupture into the pericardial sac. Of 20 cases of penetration of the diaphragm by gastric ulcer, collected by Pick, in 10 the ulceration had perforated the pericardium.

Bright's Disease.—Pericarditis may be encountered as a complication in

any form of nephritis, but is most frequent in the acute nephritis of adults and in chronic interstitial nephritis. The opinion has long been held that this form of pericarditis is the result of a toxic state of the blood arising from a failure of the eliminatory power of the kidneys, and this view has received support from the fact that the disease has developed in many instances when the phenomena of uremia were well pronounced; but until more thorough bacteriologic studies of the pericardial effusion have been made in these cases, a complete acceptance of the uremic origin of the inflammation is unwarranted. Indeed, it is well known that local infections are of common occurrence in the course of severe visceral diseases, and it seems not unreasonable to suppose that pericarditis developing under such circumstances is often of a microbic nature. This view has received some confirmation in a study recently made by Baillet, who, in a fatal case of uremic pericarditis, obtained a pure culture of streptococci from fluid drawn from the pericardial sac two hours after death and under strict precautions to prevent any accidental contamination. On the other hand, Banti did not find any bacteria in the pericardial exudate in nephritis and uremia.

Traumatism.—Contusions of the chest, fracture of the ribs, and penetrating wounds are occasional causes of the disease. In exceptional cases the pericardium has been wounded by foreign bodies impacted in the esophagus.

Bacteriology.—The micro-organisms most commonly associated with pericarditis are the different kinds of streptococci and staphylococci, the pneumococcus, and the tubercle bacillus (see Tuberculosis of the Pericardium).

Inflammation of the pericardium is invariably accompanied by more or less exudation, and, according to the character of the latter, three principal varieties may be recognized: serofibrinous, fibrinous, and purulent.

Serofibrinous Pericarditis.—In mild forms of pericarditis the serous membrane is more or less injected and lusterless, and covered in circumscribed patches or even throughout with a delicate gauze-like membrane, which can be readily peeled off with a knife-blade. Minute extravasations are often noted, which have resulted from the rupture of new blood-vessels. The serous exudation may be inconsiderable, in which case the term *dry pericarditis* is not inappropriate. Often, however, the serum is far in excess of the fibrinous exudation, the quantity varying from a few ounces to one or more pints. The fluid presents a great variety of appearances. Most commonly it is clear, transparent, and of a yellow or greenish color. In other cases it is more or less turbid or even opaque, from the abundance of corpuscles and fibrin. The latter may float free in the form of minute particles, slender threads, or curdy flakes. Sometimes, particularly in tuberculous or cancerous cases or where the inflammation accompanies some grave cachexia, the fluid is dark red from admixture with blood (*hemorrhagic pericarditis*).

The fluid has the usual characteristics of inflammatory serum; that is, it is of an alkaline reaction, contains from four to five per cent. of proteids, and has a specific gravity averaging about 1.020. This variety of pericarditis is most frequently excited by rheumatism, Bright's disease, tuberculosis, or chorea. It may end in complete recovery by the absorption of the effusion and the subsequent restoration of the serous surfaces to a normal condition. When, however, the fibrinous exudate is present in considerable quantity, perfect resolution is rarely effected. In such cases, after

absorption of the fluid, the opposing surfaces become more or less closely knit by firm adhesions. Circumscribed deposits of fibrinous material, instead of resulting in adhesions, may leave behind, on the surface of the heart, dense white opaque patches, which have been termed *milk-spots*.

Fibrinous Pericarditis.—This variety is characterized by the exudation of comparatively little fluid, but of large quantities of fibrin. The latter is generally more abundant on the epicardium, and may be limited in distribution to the auriculoventricular grooves or the posterior walls of the ventricles; but in many instances it is widespread and involves the whole surface of the heart. It is generally of a yellowish-white color: when newly formed, it is soft and can be readily detached; but when old, it is firm and tenacious. On account of the constant action of the heart, the surface is rarely smooth, but presents a velvety, tripe-like, or shaggy texture. This appearance has often been likened to that produced when two pieces of buttered bread are brought firmly together and then forcibly separated.

In this form of pericarditis the exudation is rarely absorbed, but is organized into firm adhesions which may persist in the form of fibrous bands, uniting here and there the opposing surfaces of the pericardium, or which may be so universal as to cause a complete obliteration of the pericardial sac.

Microscopically the newly formed exudate consists of fibrillated or granular fibrin infiltrated with leukocytes. The endothelium beneath the exudate is more or less desquamated. The sub-endothelial connective tissue is crowded with leukocytes, and its blood-vessels are distended. Later the fibrinous deposit is invaded by spindle-shaped or stellate cells (fibroblasts) derived from the original connective tissue, and by new blood-vessels derived from the epicardial capillaries, and a granulation-tissue is thus formed which is ultimately converted into fibrous adhesions.

Purulent Pericarditis.—Purulent effusion in the pericardium usually follows general pyemic infection or a suppurating process in some neighboring structure; but pneumonia, tuberculosis, and the acute specific diseases not infrequently excite it. It is more common in children than in adults. The amount of pus varies from a few ounces to two or three pints. It may be thick and creamy, but it is often more limpid from admixture with a certain proportion of serum (*seropurulent pericarditis*).

A variable amount of soft fibrin is found floating in the pus and closely attached to the surface of the heart. In rare instances the pus undergoes decomposition and acquires a fetid, disgusting odor (*putrid pericarditis*).



FIG. 162.—Acute fibrinous pericarditis.

Purulent pericarditis usually terminates fatally during the progress of the disease; it must be admitted, however, that recovery may take place in rare instances, even without evacuation of the pus. In these cases the fluid element of the exudation is absorbed, leaving a solid residue which is subsequently reduced to an amorphous mass. Finally a calcareous plate may be formed by the deposition of lime salts.

Cases are on record which have terminated in the perforation of the chest-wall or neighboring organs. Artificial evacuation of pus, when successful, results in fibrous union of the pericardial surfaces.

Fibrous Pericarditis.—This form is essentially chronic, and is most commonly observed in children and young adults. It generally results from the organization of the fibrinous deposits formed in acute and subacute attacks of pericarditis, but in some instances its onset is quite insidious. According to the extent and distribution of the fibrous overgrowth, four subdivisions of the forms of pericarditis may be recognized:

1. In this group are included those cases in which the adhesions are only partial and exist as fibrous bands of various lengths, uniting here and there the two surfaces of the pericardium. The length of these filaments being determined more or less by the radius of the heart action, the longer ones are usually found near the apex and the shorter over the auricles. Sometimes the contractions of the heart serve to detach one end of a filament, so that it lies free in the pericardial sac. The pericardium itself is usually somewhat thickened and indurated.

2. In some instances the adhesions are so extensive that the pericardial surfaces are universally adherent and united to the heart, the sac being completely obliterated. To this condition the term *adherent pericardium* has been applied. When recent, the adhesions are friable, and with care the surfaces can be separated; but when old, they become exceedingly tough, and separation cannot be effected without tearing away some of the cardiac muscle. The pericardium itself is often considerably thickened, so that the fibrous covering of the heart may measure from a quarter- to a half-inch in thickness. Very rarely calcification follows, converting the whole mass into a bony capsule.

3. There is a group of interesting cases in which the adhesions are not confined to the pericardial sac, but involve also the external surface of the pericardium, thus firmly uniting the heart to the chest-wall, pleura, diaphragm, or mediastinal structures. This condition has been termed *indurative mediastinopericarditis* or *external pericarditis*. It is more common in adults than in children, and of 36 cases analyzed by Whipple, 28, or more than two-thirds, were in males. The origin of the affection is often obscure. In only a few cases has there been a definite history of a previous attack of acute pericarditis.

Undoubtedly tuberculosis of the mediastinal lymph-glands, lung, or pleura has often played an important part in its development.

Some cases have followed traumatism or one of the acute fevers, most commonly scarlatina or measles.

The fibrous hyperplasia is not always confined to the chest, but often extends below the diaphragm and involves the peritoneum, especially those portions reflected over the liver and spleen.

In a few instances, as in a case cited by Roberts, the adhesions have been entirely external, the pericardial sac being free throughout. In 11 of 36

cases collected by Whipham there was enlargement of the heart ; in nearly every instance there was enlargement of the liver from venous congestion ; in 5 cases there was enlargement of the spleen ; and in 11 of the 21 cases in which the subject was alluded to, serous effusion accompanied the proliferative peritonitis.

4. Occasionally cases are observed in which there are few if any adhesions, either internal or external, the pericardial layers alone being the seat of fibrous overgrowth.

Effects and Associated Conditions.—The disturbance produced by effusion in the pericardium cannot be said to be altogether proportionate to the quantity, since often at the autopsy several ounces of fluid are found in the sac, whereas nothing in the clinical history has suggested its presence. When, however, the amount of fluid is considerable, certain mechanic effects necessarily follow from pressure upon the chambers of the heart, the large vessels communicating with it, and even contiguous structures.

Changes in the myocardium are rarely absent, and it is to these, more often than to the lesions of the pericardium itself, that the serious sequels of pericarditis are to be attributed. As a rule, only that portion of the heart-muscle adjacent to the pericardium, inward to a depth of 1 or 2 mm., is affected ; but at other times the lesions are more general and involve the entire myocardium. The fibers are the seat of fatty and parenchymatous degenerations, and the connective tissue between them is infiltrated with round cells. At a later period the appearances are those of fibrous myocarditis. While these changes are undoubtedly often secondary to the pericarditis, there are times when they are so disproportionate to the latter and so far removed from the surface as to warrant the belief that they have developed coincidently from the action of the same morbid agent which has invaded all the structures of the heart, including not infrequently the endocardium. Fibrous pericarditis, especially indurative mediastinopericarditis, is often associated with considerable hypertrophy or dilatation of the heart, but not so commonly as formerly supposed. Enlargement was present in but 11 of the 36 cases tabulated by Whipham. The cause of this enlargement has evoked considerable discussion ; it seems likely, however, that the factor responsible for its production is not always the same. Broadbent believes that dilatation results from the myocarditis accompanying the original attack of pericarditis, and that subsequent organization of the adhesions effectually prevents the heart from again recovering its normal size. In some instances coexisting valvular disease or constriction of the large vessels by fibrous bands may be an important factor in bringing about enlargement. Finally, it is not improbable that the mere impediment offered to the movements of the heart by adhesions to contiguous structures may be productive of hypertrophy.

The right ventricle is usually more seriously affected than the left, and, according to Broadbent, for the following reasons : First, the right ventricle, on account of its weak contractile power, is less able to free itself from adhesions while in process of formation, and, when adhesions are formed, less able to contract against them and fully complete the systole ; secondly, the thin-walled right ventricle has less chance of recovering from the effects of myocarditis than the left, where there is much greater thickness of muscular substance ; and thirdly, as adhesions are more apt to unite the heart

in front to the chest-wall and below to the diaphragm than behind to the vertebral column, it follows that the right ventricle, from its anatomic relations, must suffer more than the left.

Occasionally, instead of enlargement of the heart, there is atrophy or hypoplasia. This condition has been noted most frequently where the pericarditis has occurred in early childhood, and has led to the formation of dense adhesions which have obliterated the sac of the pericardium, and so compressed the heart as to arrest its growth.

Pericarditis is often associated with endocarditis, particularly in children. It is possible for either affection to be primary, and the other secondary; generally, however, the two are to be considered as having resulted independently from the action of the same agent.

Tuberculosis.—Tuberculosis of the pericardium, when not a part of a general infection, is usually secondary to tuberculosis of the lungs or of the mediastinal lymph-glands. The condition may be acute or chronic, and the exudation may be serofibrinous, fibrinous, purulent, or hemorrhagic. There may be a marked production of new tissue and more or less distinct tubercles. There is often but little in the gross appearance of the lesions to indicate the tuberculous nature of the affection, and doubtless many of these cases have been regarded as nontuberculous and caused indirectly from exposure to cold and wet. But, as in the case of pleurisy, it seems highly probable that many cases of so-called primary pericarditis are the result of tuberculosis. It is true that tubercle bacilli are rarely discovered in the exudation; but it is now well recognized that pleurisy with an apparently sterile effusion is usually tuberculous. Eichhorst proved this to be true by inoculating guinea-pigs with large quantities (15 c.cm.) of the serous exudate. In this way 15 of 23 cases of acute pleurisy were shown to be tuberculous. In an earlier series of experiments the results were not so conclusive, as the quantity of exudate injected (1 c.cm.) was too small. In a similar manner the same investigator has shown that pericarditis is also frequently tuberculous, positive results having been obtained in 8 of 27 cases. He points out that, as the tubercle bacilli are often very scanty, ordinary culture and inoculation experiments are unreliable.

There is also a chronic obliterative pericarditis due to tuberculosis. It may, however, be impossible to determine the tubercular character without microscopic examination.

Actinomycosis.—Occasionally actinomycosis of the lungs, esophagus, mediastinum, or abdomen extends to the pericardium, whence it may invade the heart-muscle.

Tumors.—Tumors of the pericardium are rare. Carcinoma may invade the pericardium either by extension or metastasis. A few cases of primary sarcoma are recorded. J. C. Williams¹ has described a remarkable case of primary diffuse sarcoma of the parietal pericardium.

THE MYOCARDIUM.

Retrogressive Changes.—Atrophy and Hypoplasia of the Heart.—In atrophy of the heart, the organ is diminished in weight and size, from a loss of muscular substance. In hypoplasia, it has failed to reach its normal size, from defective development.

¹ *New York Med. Jour.*, April 14, 1900.

Atrophy may be total, involving the whole heart; or partial, involving certain chambers. Total atrophy occurs in the course of wasting diseases, such as cancer, phthisis, and diabetes. It is also an accompaniment of old age. Fibrous pericarditis occurring in young children may give rise to such dense adhesions that the heart is strangled and thereby effectually prevented from attaining its normal size. On account of a deficient blood-supply, partial atrophy affecting the left ventricle is sometimes observed in mitral stenosis. Finally, slowly developing stenosis of the coronary arteries is occasionally followed by partial atrophy.

As Virchow pointed out, hypoplasia of the heart and arteries is sometimes associated with chlorosis; but, apart from chlorosis, the heart is now and then found to be disproportionately small in subjects who during life gave no evidence of cardiac insufficiency.

In atrophy the heart is usually diminished in size as well as in weight. According to Wunderlich, an adult heart is to be considered atrophic that weighs less than 200 grams. Bramwell has recorded a case in which the heart weighed only $2\frac{1}{2}$ ounces (69 grams). The surface is often wrinkled, while the arteries are remarkably tortuous—appearances which are not observed in hypoplasia. The color of the muscle is variable; very often, however, it is quite brown from the deposition of pigment about the nuclei of the fibers (*brown atrophy*). A relative or actual increase of fibrous tissue may give to the walls of the heart an unnatural toughness. The pericardial sac often contains an excess of serous fluid.

Microscopic degenerative processes are always found to be associated with atrophy of the fibers. The latter in many places have lost their striations and are the seat of more or less extensive pigmentation and degeneration. Proliferation of the connective tissue is a marked feature in many instances.

Parenchymatous Degeneration.—Parenchymatous degeneration or cloudy swelling of the heart occurs in acute infectious diseases, like typhoid fever, diphtheria, septicemia, etc. It seems to be the result of a reaction between the cell protoplasm and the specific toxins of these affections. Whether high temperature itself can accomplish this transformation is an open question; it is probable, however, that the chief factors in effecting the change are poisons, even though they are in some instances the product of the febrile process rather than its cause. The changes peculiar to cloudy swelling are so intimately associated with other lesions of a degenerative or inflammatory character that it is often difficult to decide where the process begins and where it ends. As a simple transformation, it results in a swelling of the fibers, a disappearance of their striæ, and the deposition of fine granules, which, unlike fat, resist the solvent action of ether, but disappear on the addition of acetic acid. When these changes are not too profound, restoration of the cells to their normal condition is possible. When, however, the cause is severe and its action prolonged, disintegration becomes more pronounced, and other degenerative changes, such as fatty and hyaline, assist in the destruction of the cytoplasm. Finally, as an evidence of reaction, there is often present a round-cell infiltration of the intermuscular connective tissue.

When parenchymatous degeneration is well advanced and widespread, it may be revealed by certain macroscopic changes; the heart is pale and dull, its tissue is soft and flabby, and not infrequently its chambers are somewhat dilated.

Fatty Infiltration.—Fatty infiltration of the heart consists in an inordinate accumulation of fat upon the surface of the heart as well as between its muscular fibers. It is simply an excess of the fat which is normally

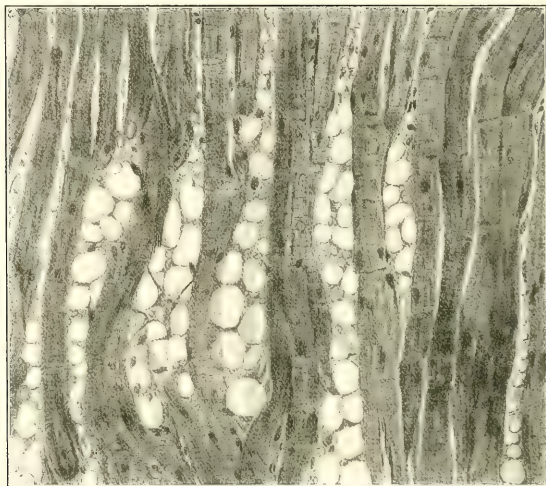


FIG. 163.—Fatty infiltration of the heart.

present in variable amounts beneath the epicardium, especially along the blood-vessels and in the grooves between the auricles and ventricles.



FIG. 164.—Fatty infiltration of the heart-muscle. The fat is stained orange with sudan III. The muscle-fibers are compressed.

As a morbid condition, it is most frequently observed as a part of general obesity in persons of advanced years. In some instances, it is due to the defective oxidation resulting from anemia or chronic pulmonary disease. When the infiltration is well marked, a large part of the heart, including

the entire right ventricle and a considerable portion of the left ventricle, may be encased in a thick capsule of fat. Over the base of the ventricles, where the most extensive deposits occur, there may be a distinct lobular arrangement. From the epicardium, fatty trabeculae may extend along the intermuscular fibrous septa as far as the endocardium, the amount gradually diminishing from the surface inward. Microscopic collections of fat-cells are everywhere interposed between the muscle-fibers. A high degree of fatty infiltration may exist for some time without affecting the integrity of the muscular substance of the heart; but ultimately, owing to compression of the muscle by the adipose tissue and to interference with its contractility, the fibers atrophy and become the seat of a true fatty metamorphosis. Rupture of the heart may take place from the replacement of the muscular walls by adipose tissue.

Fatty Degeneration.—The causes leading to the formation of fat in muscle-fibers of the heart are both local and general. The most important local cause is ischemia, from stenosis of the coronary arteries. The hypertrophied heart of chronic valvular disease is often the seat of more or less fatty changes of this kind; and, while the latter is usually regarded as the cause of the failing compensation, the possibility of its being, at least in part, the result of the cardiac insufficiency must be borne in mind. It is often observed in the outer layers of the myocardium in pericarditis.

The two general causes of true fatty metamorphosis of the heart-muscle are certain poisons and cachectic states. As examples of the former may be mentioned the toxins of various infectious diseases, such as diphtheria, scarlatina, and typhoid fever, and many mineral poisons, notably phosphorus, arsenic, and antimony. In the cachectic states are included all diseases which are associated with profound alterations in the blood, such as pernicious anemia, cancer, and phthisis. In some of these affections, however, the likelihood of a toxic action also must be considered.

Morbid Anatomy.—Fatty degeneration may be diffuse or circumscribed. Even when the cause is general, certain parts of the heart are usually more affected than others. As a rule, the ventricles, especially the left, are most seriously involved. The heart may be of any size, though naturally the tendency is toward dilatation. The macroscopic appearances are sometimes deceptive, and a heart that appears normal may show microscopically well-marked fatty changes. A change in color, however, from a dull yellowish-brown to a distinct yellow is generally observed. These colors may be uniform throughout or appear in streaks. The muscle is soft and flabby, and when cut imparts a greasy feel to the fingers. When the process is well advanced, the consistence of the organ is so much diminished that the tissue can be readily torn by the fingers. Indeed, in some instances, the immediate cause of death has been rupture of the heart under severe physical exertion.

Microscopically the muscle-fibers are found to be studded with fat droplets; these occupy the interfibrillary sarcoplasm and are disposed in rows

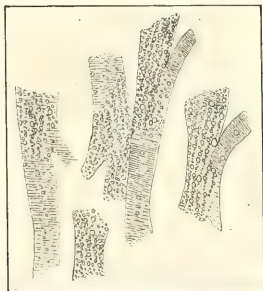


FIG. 165.—Muscle-fibers of the heart, showing fatty degeneration.

extending from the poles of the nucleus. The transverse striations are not necessarily affected; but when the condition has reached an advanced stage, the striæ as well as the nuclei may be obscured by fat. According to Goebel, these changes are usually most pronounced immediately beneath the epicardium and endocardium. In the acute infections, fatty changes in the muscle of the heart are always associated with other lesions, the most important of which are parenchymatous degeneration, vacuolization of the fibers, enlargement and segmentation of the nuclei, segmentation along the lines of the cement substance ("*myocardite ségmentaire*"), and small-cell infiltration in the interstitial tissue.

In chronic cases, especially when the exciting cause has been sclerosis of the coronary arteries, the fibers are often atrophied and pigmented, and separated here and there by extensive deposits of fibrous tissue (chronic interstitial myocarditis).

Amyloid Degeneration.—Small areas of amyloid degeneration are not infrequently met with in the heart, but the process is rarely sufficiently extensive to be recognizable by the naked eye. As in other organs, the degeneration attacks the walls of the blood-vessels and the interstitial tissue. When the endocardium and pericardium also are involved, the size and weight of the heart may be considerably increased, and the amyloid deposits may be manifested macroscopically as nodules or seams composed of a dense, grayish, translucent material. An interesting case of this kind has been recorded by Ziegler. The patient was a woman of about fifty, who had died of heart failure. On postmortem examination it was found that the heart, all the mucous membrane, the peritoneum, tongue, and lungs were amyloid. The heart-muscle and the endocardium and pericardium were everywhere thickened and beset with numerous translucent, gristly nodules as large as millet seeds.

Other lesions are usually associated with amyloid degeneration, such as interstitial myocarditis, atrophy of the muscle-fibers, and fatty or hyaline metamorphosis.

Hyaline Degeneration.—Hyaline degeneration of the myocardium is characterized by the deposition of a clear, glass-like substance in the intermuscular connective tissue. It resembles amyloid degeneration, with which it is sometimes associated; but the hyaline material has not the same staining peculiarities as the amyloid. The affected areas may be either quite homogeneous or composed of close aggregations of minute semitransparent drops. Zenker, Rosenbach, Romberg, and others have described a transformation in the muscle-cells of the heart, after various acute infections, which they regard as a form of hyaline degeneration. The fibers are swollen and translucent, and the striæ are indistinct or lost. These changes are accompanied by fatty changes, cloudy swelling, and acute interstitial myocarditis.

Lesions of the Myocardium caused by Acute Infectious Diseases.—It is a well-established fact that acute infectious diseases, such as diphtheria, scarlatina, typhoid fever, and septicemia, may produce extensive alterations in the myocardium without necessarily involving the endocardium or pericardium. These alterations affect the muscular substance, interstitial tissue, blood-vessels, and nervous mechanism of the heart.

Allusion has already been made to the frequent occurrence of parenchymatous, fatty, and hyaline changes of the cytoplasm in acute specific diseases; other changes, however, involving the muscle-nuclei, have been

described by Oertel, Romberg, and others. These observers have found the nuclei enormously distended and elongated, or divided into numerous segments. The significance of these peculiar nuclei has not been determined, but Romberg and Ehrlich agree in regarding them as evidence of degeneration and not of multiplication. In addition to these changes, vacuolization and segmentation of the muscle-fibers are frequently seen.

The most important lesion of the interstitial tissue consists in its infiltration with round cells, either singly or in groups. These cells are found most abundantly about the blood-vessels, but their appearance inside of the muscle-bundles has been repeatedly observed. Romberg attaches considerable importance to this lesion. He believes that in cases of recovery from the acute diseases it may be followed by the formation of circumscribed fibrous patches, which may seriously impair the function of the heart and ultimately induce secondary change in the myocardium similar to those resulting from stenosis of the coronary arteries.

Important changes are sometimes observed in the blood-vessels of the myocardium; thus, there may be swelling of the intima, hyaline degeneration of the media, and leukocytic infiltration of the adventitia. The capillaries are overdistended, and small extravasations beneath the pericardium and into the parenchyma are not rare. The most significant vascular lesion, however, consists in the presence of hyaline thrombi in the small arteries. The effect of these occluding thrombi on the functional activity of the heart can be readily appreciated.

Only a few observations have been made concerning the changes wrought in the nervous mechanism of the heart by the specific fevers. In some cases the ganglia have been infiltrated with round cells; in other instances the ganglion-cells have shown a loss of their nuclei and fatty changes.

Segmentation and Fragmentation of the Myocardium.—Segmentation of the muscle-fibers, although alluded to by earlier writers, particularly by Zenker, was first carefully studied in 1877, by Renaut and Landouzy, who described it under the name of *état ségmentaire*. Lately it has received the attention of numerous investigators; in this country, of Hektoen¹ and J. B. MacCallum² especially. The frequency of its occurrence is attested by the fact that Tedeschi found it in 48 per cent. of 236 deaths from various causes, and Hektoen in about 65 per cent. of 190 consecutive cases in which an examination was made. A distinction is made between segmentation, which consists in separation along the natural line of union between the muscle-cells, and fragmentation, which consists in rupture of the fiber at any part of its course without reference to the cement lines. The two processes are usually associated, though not necessarily so.

Segmentation is very commonly found in the heart after sudden death from traumatism or suffocation, in connection with hypertrophy from its usual causes, and after many acute infections. The process may be local or general. The parts most frequently affected are the papillary muscles of the left ventricle and the septum. It is rare in the auricles. The appearance of the heart is variable and is dependent largely upon associated morbid conditions. When segmentation is the only lesion present, the organ may not appear abnormal. Very often changes characteristic of parenchymatous degeneration, of brown atrophy, or of chronic interstitial myocarditis are present. In simple dissociation the segments may consist of single cells or

¹ *Am. Jour. Med. Sci.*, Nov., 1897.

² *Jour. Exp. Med.*, iv., 409-424, 1899.

of isolated masses composed of a number of cells. While the ends are sometimes clean-cut, they often show uneven contractions or extensions.

The exact significance of segmentation is still undetermined; some pathologists regard it as a purely agonal or postmortem change, while others look upon it as an intravital process depending upon causes which have directly affected the integrity of the intercellular cement or which have influenced the latter by inducing nutritive changes in the muscle-cells. Hektoen closes an elaborate study of the subject with the following summary:

“The cardiac muscle-fibers frequently separate into muscle-cells and irregular fragments. Segmentation and fragmentation are due to disproportion between the vigor and order of muscular contraction and muscular cohesion. They occur in normal heart-muscle due to excessive vigorous and irregular contractions. More frequently they are encountered in association with acute and chronic secondary and primary myocardial changes that

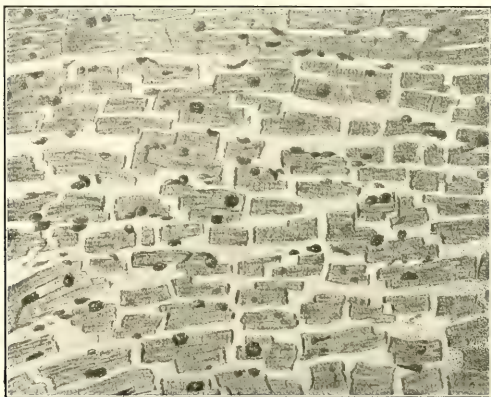


FIG. 166.—Segmentation of the heart-muscle.

alter the cement, weaken the plasma, and predispose to dissociation under normal or increased heart's action. General segmentation is of brief duration, because its occurrence is incompatible with further cardiac contractions. Local or limited segmentation may perhaps cause incompetency of the auriculoventricular valves, especially the mitral. It may lead to cardiac insufficiency and possibly to rupture of the heart. The fate of loosened muscle-cells is not known. It seems, however, that local dissociation is of but short antemortem duration. The occurrence of primary segmentation as a distinct disease is not known.”

Progressive Changes.—Hypertrophy and Dilatation.—Hypertrophy and dilatation of the heart can be conveniently discussed together, since they are so frequently associated and since the causes of the one, with certain limitations, are the causes of the other.

Hypertrophy is enlargement of the heart, due to an increase of the muscular substance of the organ. It may be total, involving all parts of the

heart; or partial, involving certain chambers of the organ. Dilatation is increase in the size of the cavities of the heart, with or without thickening of their walls. Like hypertrophy, it may be total or partial.

Increased demands upon the function of the heart lead to hypertrophy or dilatation, the tendency to the one or the other being determined by the suddenness of the demand, its intensity, and the tone of the cardiac walls. Increased demands upon the entire heart, long-continued tachycardia, or frequent attacks of palpitation, such as occur in exophthalmic goiter or result from the excessive use of tobacco, may cause total hypertrophy. The latter is also observed in interstitial myocarditis and adherent pericardium. Prolonged physical exertion, while it often enlarges the whole heart, more particularly affects the left ventricle; and the same is true of chronic Bright's disease. The manner in which nephritis induces cardiac hypertrophy has long been under discussion, but our knowledge of the relation between the two affections has not advanced materially beyond the hypotheses formulated by Bright nearly fifty years ago. Bright says: "The obvious structural changes in the heart have consisted chiefly of hypertrophy, with or without valvular disease; and what is most striking, out of 52 cases of hypertrophy, no valvular disease whatsoever could be detected in 34; but in 11 of these 34, more or less disease existed in the coats of the aorta; still, however, leaving 22 without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some local cause for the unusual efforts to which the heart has been impelled; and the two most ready solutions appear to be either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately, or that it so affects the minute capillary circulation as to render greater action necessary to force the blood through the distant subdivisions of the vascular system."

The continued use of alcoholic beverages, a practice common among those who work in breweries, is productive of enlargement of the heart. Bollinger has recorded 42 cases of simple hypertrophy, without valvular diseases, which occurred among the workmen of Munich, and attributes the condition to the stimulating effect of the alcohol on the heart, to the overfilling of the vessels, and to increased nutrition.

Occasionally the ventricular walls are considerably thickened in still-born infants. Such a condition, existing without other circulatory abnormalities, is regarded by Virchow as a myomatous neoplasia of congenital origin.

Increased Demands upon the Left Ventricle.—Lesions affecting the aortic orifice are invariably followed by hypertrophy of the left ventricle. In stenosis the enlargement is due to the difficulty offered to the unloading of the ventricle; and in insufficiency, to the increased quantity of blood to be propelled from the chamber. Stenosis of the aorta (congenital or acquired) and general arteriosclerosis induce hypertrophy of the left ventricle. According to the investigations of Hasenfeld, arteriosclerosis only leads to hypertrophy of the left ventricle when the thoracic aorta or the splanchnic vessels are severely affected. Arteriosclerosis of the other vessels does not seem to have the same effect.

Increased Demands upon the Right Ventricle.—Lesions affecting the mitral orifice, and diseases of the lungs which interfere with the free entrance of blood from the heart, such as emphysema and fibrous pleurisy, are the

most common causes of hypertrophy of the right ventricle. Stenosis of the pulmonary orifice or of the pulmonary artery is a rare cause. In adherent pericardium the right ventricle is usually more affected than the left, for the reasons already given.

In the auricles hypertrophy is always associated with dilatation. Enlargement of the left auricle is usually dependent upon mitral disease, especially stenosis; and enlargement of the right auricle, upon some disease which obstructs the pulmonary circulation, or more rarely upon tricuspid stenosis.

Dilatation of the heart may precede hypertrophy or follow it. In the main dilatation is due to the same causes as hypertrophy; but it is more apt to develop than the latter when the strain is very severe and arises suddenly, or when the muscular wall of the heart is seriously affected. Interstitial myocarditis, even more than fatty changes, is the chief factor in lessening the resistance of the myocardium to the point where increased intracardiac pressure brings about dilatation of the cavities. That dilatation may follow hypertrophy without the appearance of microscopic lesions in the cardiac muscle is likely. Indeed, the microscopic changes in some instances may be the result of the failing compensation, instead of its cause. It seems likely that Cohnheim's view is correct, and that sometimes there is a simple fatigue or exhaustion of the fibers, unattended by any demonstrable histologic change. The inflammatory and nutritive changes in the myocardium incident to the infectious fevers not infrequently result in simple dilatation.

Morbid Anatomy.—Three varieties of cardiac enlargement may be recognized: (1) Simple hypertrophy, a form in which the muscle is thickened, but in which the cavity is of normal size; (2) excentric hypertrophy, or hypertrophy with dilatation, which is characterized by thickening of the muscle and an increase in the size of the cavity; (3) simple dilatation, in which there is thinning of the muscle and an increase in the size of the cavity. Some writers speak of a concentric hypertrophy, a form in which the muscle is thickened and the cavity is diminished in size; but such a condition seems to be more apparent than real, and is generally attributed to postmortem contraction.

The average normal weight of the heart in the adult is between 250 and 300 grams; in hypertrophy, however, the weight may increase threefold or even fourfold. A weight of 1980 grams in a case recorded by Stokes has probably not been surpassed. In simple and excentric hypertrophy, the thickness of the walls is often considerably increased. The wall of the left ventricle, instead of measuring from 7 to 10 mm., may measure from 20 to 25 mm.; and the wall of the right ventricle may be increased in thickness from a normal measurement of from 4 to 5 mm. to from 10 to 20 mm. The papillæ and trabeculæ usually share in the enlargement. The shape of the heart is also changed, according to the seat and degree of the enlargement. When the left ventricle is especially involved, the heart is elongated and extends more to the left. In enlargement of the right ventricle, the heart is increased in width and becomes more globular in form. The color and consistence of the muscle vary considerably, according to the state of nutrition. When quite healthy, the muscle is of a deep-red color and is resistant to the knife; when cut, the edges remain widely separated. Sometimes the color is more or less brown from pigmentary infiltration, or yellow from

fat. Fibrous changes make the muscular substance tough, while fatty changes make it friable.

Microscopically the individual muscle-cells are increased in size, and their number is probably also increased. Associated with the hypertrophy, there is often more or less connective-tissue hyperplasia or fatty degeneration.

Lesions of the Coronary Arteries.—Lesions of the coronary arteries play an important role in the production of myocardial disease. Being terminal arteries, occlusion of their branches by embolism, thrombosis, or arteriosclerosis throws the burden of sustaining nutrition in the affected part upon the neighboring capillaries and the vessels of Thebesius, which are usually so unequal to the emergency that degeneration or necrosis ensues.

Embolism and Thrombosis.—Complete occlusion, though it may be produced slowly by sclerotic changes, is usually the result of embolism or thrombosis. The location of the orifices of the coronary arteries near the root of the aorta, the angle at which these vessels diverge, and the force of the current at this point, are conditions which render the entrance of emboli of infrequent occurrence. Nevertheless, obstruction from this cause is occasionally encountered. The embolus usually consists of a piece of fibrin detached from one of the valves, especially the aortic, or from a cardiac thrombus; but occasionally it is made up of atheromatous pulp which has escaped from the vessel-wall some distance above the point of occlusion. The favorite location of emboli is in the anterior branch of the left coronary artery.

Thrombi are more common in the coronary arteries than emboli. Their formation is favored by sclerotic changes in the vessels; and, like emboli, they are most frequently found in the anterior branch of the left coronary artery.

Sudden occlusion of a large coronary branch may be followed by instant death; the cause of which, according to Porter, is the interruption of the entire cardiac circulation and the arrest of the heart in fibrillary contractions. When the obstruction does not prove immediately fatal, it may give rise to an area of anemic necrosis (*myomalacia cordis*), the favorite location of which is the wall of the left ventricle near the apex.¹ When recent such areas are irregular in outline, firm, slightly elevated, and of a yellowish color. Subsequently the patch softens and falls slightly below the surface of the heart. The endocardial surface of these infarcts is often covered with soft thrombi. Microscopic examination of the affected tissue reveals muscle-fibers in various stages of degeneration and disintegration, molecular debris, red and white blood-cells, and pigment granules. The appearance of granulation-tissue at the periphery is an evidence of regeneration. Such an area, if extensive, may end in rupture and the escape of blood into the pericardial sac; or, coincident with the absorption of the dead matter, new connective tissue may enter from the periphery and subsequently replace the anemic infarct with a fibroid cicatrix.

These circumscribed indurations are often of such a size that they can be readily recognized; on the other hand, small ones embedded in the heart-muscle are in danger of being overlooked unless the organ be thoroughly and systematically sliced. Finally, since the cicatricial tissue is less resistant

¹ For an experimental study of infarction of the heart, see Baumgarten, *Am. Jour. of Phys.*, ii., 243-264, 1899.

than normal muscle, a large scar may yield to the blood-pressure and form an aneurysmal dilatation.

Arteriosclerosis.—Sclerosis of the coronary arteries arises from the same causes which lead to sclerosis in other vessels. The obstruction occasioned by this condition develops slowly and leads usually to fatty degeneration of the heart, chronic interstitial myocarditis, or both. The stenosis may be more or less uniform throughout the vessels; or again, the constriction may be confined to the orifices, the main trunks, or the terminal branches. Chronic interstitial myocarditis, or fibroid induration of the heart, represents a replacement fibrosis: atrophy and destruction of the muscle being accompanied by a compensatory hyperplasia of the connective tissue. The process is usually most marked in the wall of the left ventricle near the apex, or in the septum. When diffuse, it is often associated with extensive hypertrophy.

Aneurysms of the Coronary Arteries.—Aneurysms of these vessels may result from sclerosis or embolism. They may be single or multiple, and vary in size from that of a millet seed to that of a cherry. Quinke reports a case in which he found twenty, varying in size from that of the head of a pin to that of a bean. The usual termination is rupture, generally into the pericardium, but occasionally into the ventricle, as in a case observed by Aran.¹

Aneurysm of the Heart.—The term aneurysm of the heart is applied to local dilatation of the cardiac walls or to pouch-like projections of the valves. While dilatation of an entire chamber of the heart is common, aneurysm is rare. Any lesion which diminishes the resistance of the muscle in localized areas may lead to this condition.

Aneurysm of the walls is usually due to the fibrous myocarditis resulting from coronary obstruction or to gummatous infiltration. Wounds of the heart, acute mural endocarditis, and fatty degeneration are rare causes. Rupture, however, is a more common termination of the last two conditions than local dilatation. According to Grandmaison, chronic adhesive pericarditis may be productive of aneurysm both by inducing fibrous myocarditis and by making traction on the walls. The anterior wall of the left ventricle near the apex is the usual seat. In 59 of 90 cases collected by Legg, it was in this situation. The septum is involved next in frequency; and when located here the aneurysm usually projects into the right ventricle on account of the greater force of the blood-current behind it. The walls of the right ventricle and of the auricles are very rarely affected; in only 3 of Legg's cases was the right ventricle the seat of the lesion. In size, aneurysms vary from that of a marble to that of the heart itself. Usually there is a single pouch communicating with the cavity of the heart by a large orifice, but in some instances the dilatation is saccular and the opening very small. A few cases have been recorded in which the aneurysm consisted of a series of intercommunicating sacs. The parietal layer of the pericardium is usually adherent to the sac, the walls of which represent the three layers of the heart, more or less replaced by fibrous tissue. The parietes of large sacs may be as thin as paper and completely devoid of muscle-fiber. Thrombi are usually found in the interior; they may be soft and granular or firm and laminated. The terminations are variable. In some instances, after reaching a certain size, they remain stationary. A few cases have been recorded

¹ See article by Capps, "Aneurysms of the Coronary Artery," *Am. Jour. Med. Sci.*, Sept., 1899.

in which the sac has been found completely filled with a firm clot. In a case of this kind reported by Wilkes the contents had undergone calcification. Very often, death results from cardiac insufficiency: to which, however, the aneurysm may be only contributory. It is remarkable how rarely rupture occurs, only seven of Legg's cases having ended in this way.

The dissecting aneurysm of the heart is an interesting form. It usually originates at the aortic orifice from ulcerative processes or traumatic rupture, and extends into the periaortic space of Vestberg.¹ Aneurysms in the beginning of the aorta may extend into the walls of the heart and become dissecting by secondary rupture. Vestberg distinguishes interparietal, septal, parietal, and valvular dissecting aneurysms of the heart.

Aneurysms of the valves may be acute or chronic, single or multiple. They are usually the result of ulcerative endocarditis; but sclerotic or atheromatous processes are sometimes responsible for their development. The bulgings are more or less spheric in shape, and project in the direction of the greater blood-pressure: those of the aortic segments protruding into the ventricle, and those of the mitral segments into the auricle. Although most authorities state that the aortic valve is much more frequently affected than the mitral, Drasche, who has carefully reviewed the literature of the subject, finds that they are more commonly located in the mitral valve, and that the anterior leaflet is more frequently affected than the posterior. Rupture of the valve, resulting in extensive insufficiency, is the usual termination in acute aneurysms. When large, they sometimes protrude into the blood-current and cause obstruction of the orifice presided over by the valve in which they are located. Small aneurysms sometimes give rise to no special disturbance, the endocarditis upon which they are dependent running its usual course.

Rupture of the Heart.—Spontaneous rupture of the heart is of rare occurrence. Krouskoff observed it but 3 times in 8000 autopsies. Mallett, writing in 1889, was able to collect only 179 authenticated cases. It is more common in men than in women. Of 115 cases tabulated by Odriozola, in 94 the age was over sixty, and in only 9 was it under fifty; but rupture of the heart has been met with as early as the tenth month. The accident has always occurred in a heart weakened by some pre-existing disease. Fatty degeneration with stenosis of the coronary arteries is the lesion usually encountered. Among the less frequent causes of rupture may be mentioned anemic necrosis from sudden occlusion of an important coronary branch, suppurative myocarditis, neoplasm, gumma, and echinococcus-cyst. In very rare instances the rupture has resulted from an affection acting upon the walls of the heart from without, as in the case recorded by McPhedran, in which an aortic aneurysm burst into the left auricle. In some cases the rupture has occurred during perfect repose, but more often mental excitement or physical exertion has been the determining factor. Thus, it has occurred during severe muscular effort, vomiting, coughing, defecation, or coitus. In one case it was excited by the passage of a stomach-tube, and in another by catheterization.

In 71 of 100 cases collected by Quain death was instantaneous. Sometimes, however, the rent is temporarily filled by blood-clot, and life is prolonged for several hours or even several days. Duplant records a case

¹ "Om dissekerande hjärtaneurismer," *Nordiskt medicinskt Arkiv.*, Ny Följd, vii., Nos. 26 and 30, 1897.

in which the patient lived ten days after perforation took place. Such remarkable instances of prolongation of life after rupture of the heart, as well as the trivial character of the injury that sometimes leads to the accident, make this condition especially interesting from a medico-legal standpoint.

The rent occurs most frequently in the left ventricle, especially on the anterior aspect near the septum. According to Odriozola, the seat of the rupture in 132 cases was as follows: Left ventricle, in 96; right ventricle, in 22; right auricle, in 10; left auricle, in 2; and the auriculoventricular groove, in 2. As a rule, there is only one rent; in a few instances, however, two or more perforations have been discovered. The size and shape of the tear are variable, and depend to a great extent upon the condition of the myocardium and the seat of the lesion. The length of the opening ranges from a few millimeters to four or five centimeters. The fissure is more or less irregular in outline, often Y- or V-shaped; it usually runs in the direction of the muscle-fibers, and for this reason the internal and external openings are not often opposite each other. Not infrequently the tear is found in the wall of a cardiac aneurysm. In the neighborhood of the opening, fibrinous deposits are usually found; and these no doubt often serve to arrest the bleeding for a limited period. The amount of blood found in the pericardial sac varies from a few ounces to a quart or more. Death can rarely be attributed to the actual loss of blood; it is probably due either to disturbed innervation or to interference with the movements of the heart from the rapid accumulation of blood in the pericardial sac.

Inflammations.—Acute Myocarditis.—Acute inflammation of the myocardium usually follows one of the acute infectious diseases, such as diphtheria, scarlatina, rheumatism, and typhoid fever. It is very often



FIG. 167.—Acute myocarditis; segmentation; leukocytes between the segments. $\times 125$.

associated with acute endocarditis or pericarditis, and no doubt plays an important part in producing the serious symptoms which sometimes arise in the course of these diseases. In certain cases, however, the myocardium is the only part affected.

The inflammatory process is always accompanied with more or less parenchymatous or fatty changes of the muscle-fibers, but it appears to bear no definite relation to the latter. The essential lesion is the infiltration of the interstitial tissue with round cells. These cells are found especially about the blood-vessels, and appear singly or in groups. The veins and capillaries are dilated and contain an increased number of leukocytes. The left ventricle and the septum are usually the parts of the heart most seriously

affected. In two cases of acute rheumatic endocarditis, Romberg found cellular infiltration and thrombosis of many small arteries of the myocardium. As these changes were mainly in the vicinity of the auricular junction, the disturbing influence on the functional activity of the valves can be readily appreciated.

As to the terminations of acute myocarditis, it is likely that mild attacks end in complete resolution and the restoration of the heart-muscle to its normal condition; on the other hand, when the inflammatory process is severe, it is highly probable that the cellular infiltration becomes the foundation of a subsequent focal sclerotic myocarditis. Such a view is supported by the observations of Ziegler, Leyden, Romberg, and Lépine.

Acute Suppurative Myocarditis.—Acute suppurative myocarditis usually occurs in the course of some pyemic affection, especially ulcerative



FIG. 168.—Acute suppurative myocarditis with miliary abscess; segmentation; cells between the segments.

endocarditis, the myocardium being involved through the entrance of infected emboli into the branches of the coronary arteries. In rare instances the disease results from the direct extension of a purulent pericarditis or malignant endocarditis. The process may be diffuse or circumscribed, the latter constituting abscess of the heart.

Macroscopically the condition is manifested by the presence of yellowish-gray spots or streaks, which may or may not be surrounded by a reddish zone of congestion. Sometimes these purulent collections are very numerous and widely distributed throughout the myocardium; but, as a rule, the left ventricle is more affected than the right. Abscesses varying in size from that of a pea to that of a marble are not uncommon. Roth reported one which contained 30 grams of pus. Microscopic examination of a small suppurating focus reveals a dense aggregation of leukocytes, disintegrated muscle-fibers,

and colonies of bacteria. In most cases abscesses of the heart are found intact, death having resulted from the disease which led to their development. In other instances rupture occurs into the pericardium or into one of the cavities of the heart. In this latter event septic emboli are carried into the circulation and give rise to metastatic abscesses in various organs, especially the spleen, kidneys, and brain. Occasionally the pus becomes inspissated and subsequently calcified. Acute cardiac aneurysm is another termination of circumscribed suppurative myocarditis. Finally, abscesses situated in the septa may establish communication between the cavities of the heart.

Chronic Interstitial Myocarditis (*Fibroid Induration of the Heart, Cardiosclerosis*).—The term chronic interstitial myocarditis is used to designate a condition in which the walls of the heart are the seat of a diffuse or circumscribed overgrowth of fibrous tissue. The affection is usually secondary to disease of the coronary arteries. Thus, in 18 of 21 cases cited by Steven, the arteries were found distinctly diseased. It occasionally happens that an area of anemic necrosis produced by the occlusion of an artery by an embolus or thrombus, instead of resulting in rupture of the heart, is gradually replaced by a new growth of fibrous tissue. More commonly, however, a slowly developing endarteritis is responsible for the sclerotic change. In some cases the obstruction is chiefly at the orifice of the vessel, the finer branches being only slightly altered; on the other hand, it is not uncommon to find a diffuse obliterating endarteritis with an orifice of nearly normal dimensions. It is questionable whether the term fibroid degeneration can be correctly applied to the fibrous hyperplasia accompanying this slow starvation of the cardiac muscle, since overgrowth of tissue can scarcely be considered a degenerative process. It is urged that it is equally inappropriate to use the term chronic myocarditis to designate an affection which is so conspicuously dependent upon a primary atrophy or degeneration of the parenchyma. It is conceivable, however, that the degenerate muscle itself may act as an irritant; and although the usual evidences of irritation may be wanting, this does not become a serious objection if we regard inflammation not as a series of unvarying phenomena, but as a process the essential factor in which is reaction to injury (Adami).

Fibrous myocarditis may be secondary to chronic endocarditis or pericarditis. In the first instance the papillary muscles are most frequently involved; in the second the superficial layers of the myocardium. In mitral disease, after a protracted period of imperfect compensation, the heart may show diffuse sclerosis with dilatation of the coronary veins and degeneration of the muscle-bundles. As a primary affection of the heart, chronic myocarditis may result from the reaction of poison of the muscle-substance to toxic agents brought to it directly through the blood. In this way the disease may be associated with chronic rheumatism, syphilis, or alcoholism. As was stated in discussing acute myocarditis, it is probable that the cellular infiltration which has been observed in the heart after typhoid fever, diphtheria, and other infections, is not rarely followed at a later period of life by focal sclerotic myocarditis.

In many instances the fibroid change is distinctly visible to the naked eye, and is manifested by grayish streaks between the muscle-fibers or as circumscribed white patches of a tough, leathery consistence. The favorite seats are the anterior wall of the left ventricle near the apex, the septum, and the tips of the papillary muscles. In some cases the fibrous change,

though quite extensive, is not so conspicuous, and indeed may be overlooked unless the wall of the heart is examined in serial sections.

Microscopic examination reveals an excess of connective tissue in the form of wavy bands running parallel with the muscle-fibers. The latter are usually more or less atrophied and often the seat of fatty or hyaline changes. When the process is well developed, it is usual to find areas of hyperplastic connective tissue devoid of muscle-cells. When associated with sclerosis of the arterioles, the tissue immediately around the affected vessels may be quite normal, while parts more remote show extensive transformation. The presence of small-cell infiltration is an indication that the process was still advancing when the patient died.

Chronic interstitial myocarditis may be associated with aneurysm of the heart, chronic endocarditis or pericarditis, hypertrophy and dilatation, or intracardiac thrombosis. Aneurysm of the heart is usually due to circumscribed cardiosclerosis, the weakened wall gradually yielding under the intracardiac



FIG. 169.—Chronic interstitial myocarditis.

pressure. It is probable that in every case of pericarditis the myocardium is involved to a greater or less depth, but in mild attacks the damage to the latter is inconsiderable; when, however, the pericarditis is of sufficient severity to cause extensive fibrous adhesions, the accompanying myocarditis is often intense enough to play an important part in developing the dilatation of the heart which is so apt to be a subsequent complication in these cases. Lesions of the valves are frequent in connection with fibroid changes in the myocardium. In some cases the two affections have developed simultaneously from the action of the same irritant. In a few instances it seems not improbable that a primary lesion of the papillary muscles has been responsible for the valvular insufficiency. Finally it has been shown that endocardial lesions themselves, by producing venous stasis, may give rise to a sclerosis having its starting-point in the vicinity of the dilated coronary veins.

Enlargement of the heart is a common accompaniment of cardiosclerosis; in one of Fagge's cases the organ weighed 35 ounces. The fibrous

overgrowth interferes with the ventricular contractions, and at the same time diminishes the resistance offered to the blood-pressure; so that the enlargement is due partly to hypertrophy and partly to dilatation.

Advanced disease of the myocardium is prone to excite the formation of intracardiac thrombi. The latter are most frequently found in the auricular appendices and in the muscular interlacement near the apex. A slight amount of fibrous change in the heart may give rise to no serious disturbance; but, when well marked, the usual termination is gradual failure of the circulation from cardiac insufficiency or sudden death in a paroxysm of angina pectoris.

Tuberculosis of the Myocardium.—Townsend, in 1832, was the first to record an example of tuberculous infection of the myocardium. In 1898 Hand collected 42 cases.¹ In nearly every instance a primary focus of tuberculous disease is found elsewhere in the body, especially in the mediastinal lymph-glands. Most of the cases have occurred before the fifteenth year. Infection may take place through the veins or by the spreading of a tuberculous pericarditis, but undoubtedly the most common avenue of invasion is through the lymphatics.

Anatomically the disease may be manifested in one of three ways: First and most frequently, as a circumscribed cheesy nodule, varying in size from that of a pea to that of a hen's egg; second, as semitransparent miliary tubercles disseminated through the cardiac muscle; and third, as a true tuberculous myocarditis, consisting of a diffuse sclerosis with giant cells and small round cells distributed between the muscle-fibers and the bands of connective tissue. The ventricles are more frequently affected than the auricles. The disease may be confined to the myocardium; but not infrequently the pericardium, and more rarely the endocardium, share in the tuberculous process.

Syphilis of the Myocardium.—Syphilis of the myocardium manifests itself as a more or less diffuse fibroid induration, as gummatous growths, or very rarely as amyloid degeneration. Fibroid induration or interstitial myocarditis is usually secondary to syphilitic endarteritis; but it probably can result from the direct action of the specific poison on the muscle-cells or their sheaths, since a few cases have been noted in which no lesion of the coronary arteries could be detected.

Gummatous growths are not so commonly found after death as syphilitic fibrosis; but it should be borne in mind that the latter condition, as well as aneurysm of the heart, quite frequently results from antecedent gumma. In the early stages gummas appear as yellowish or grayish cheesy nodules, varying in size from that of a pea to that of a marble, surrounded by a zone or capsule of dense fibrous tissue. Subsequently hardening or softening may occur, according as fibrous transformation or degeneration predominates. The wall of the left ventricle and the septum are most frequently attacked. The weakening of the muscular structure effected by the evolution of a gummatous growth is one of the causes of aneurysm of the cardiac walls. In many instances hypertrophy and dilatation of the heart, chronic adhesive pericarditis, and sclerotic endocarditis are concomitant conditions, and are usually secondary to the more important lesions of the myocardium.

Syphilis of the heart frequently ends in sudden death; 21 of 63 cases reported by Mrácék so terminated. The cause of the fatal syncope may be

¹ See also Moser, *Med. and Surg. Rep. of the Boston City Hospital*, xi., 194-203, 1900.

due to rupture of the heart or to occlusion of the coronary arteries by fibroid thickening or by an embolus derived from a softening gumma or from the contents of a cardiac aneurysm.

Foci of interstitial myocarditis occur in congenital syphilis.

Actinomycosis of the myocardium has been observed by Ponfick and others as the result of extension from the neighborhood or of metastasis.

Tumors of the Heart.—Tumors of the heart-muscle are rare; carcinomatous, sarcomatous, myxomatous, lipomatous, fibromatous, and myomatous growths are occasionally encountered. They may have their origin in the myocardium, or they may invade the latter from the pericardium or endocardium.

Carcinoma is always secondary; and sarcoma, with very rare exceptions, is also secondary. They may be single or multiple, and may appear as projecting nodules or as diffuse granular plates. Sarcoma is not infrequently secondary to a primary growth in the mediastinum, the pericardium being first invaded and then the cardiac walls. Osler describes a remarkable case of sudden death in a child in whom he found the tricuspid orifice firmly blocked by a sarcomatous mass that had come from the renal vein, the latter being filled with a sarcoma extending from a large tumor of the kidney.

Rhabdomyoma is congenital and occurs often as multiple tumors. The structure resembles that of embryonal heart-muscle.

True myxomatous tumors are occasionally observed, but most of the cystic formations found within the heart are softened thrombi. Polypoid growths are sometimes found protruding from the walls of the heart; most of these are organized thrombi, but others are of different origin, usually springing from the left auricular septum, and often, as in 6 of 11 cases collected by Pawlowsky, projecting through the mitral orifice into the ventricle. They are of a reddish color, and are covered by a smooth, shiny membrane. In addition to blood-constituents and fibrin, they often contain connective tissue and blood-vessels. The origin of these cardiac polyps is obscure; some have apparently consisted of varicose veins filled with organized clot, while others seem to have been the result of a hemorrhagic extravasation beneath the endocardium.

Small tumors of the heart may occasion no disturbance; but large growths may excite dilatation, valvular insufficiency, rupture, or embolism.

Animal Parasites.—In man the heart-muscle is rarely invaded by animal parasites; but the *Cysticercus cellulosæ*, *Pentastomum denticulatum*, and *Echinococcus* are occasionally seen. The last only is productive of mischief. In 155 cases of infection by the *Cysticercus cellulosæ*, Stiles found the parasite in the heart in 9 instances. In the 100 cases of echinococcus diseases occurring in the United States, compiled by Sommer, the heart was involved but once; but among 160 cases in which Davaine found echinococci in organs other than the liver, in 10 they were found in the heart.

Hydatid cysts vary in size from that of a pin-head to that of an orange, and may be single or multiple. They are more frequently found in the right ventricle than in the left. They sometimes rupture into the pericardium, or more commonly into one of the chambers of the heart, the contents being discharged through the aorta or the pulmonary artery. Oesterlen found the sac ruptured in 6 of 21 cases. In one instance gangrene of the right leg followed plugging of the femoral artery by hydatid vesicles discharged into the circulation from the rupture of a cyst in the left auricle.

THE ENDOCARDIUM.

Intracardiac Thrombi.—It is exceptional not to find at the necropsy a certain amount of coagulated blood in at least one of the chambers of the heart. This clot is most frequently found in the right auricle or ventricle, and is probably formed after death; although it is generally assumed, but without any evidence, that coagulation may occur also during the agonal period. Postmortem clots have certain characteristics by which they may be distinguished from thrombi; they are yellow or red, often particolored, the upper part being pale yellow and the dependent part dark red. They are soft, moist, translucent, and elastic; and being nonadherent, though often wrapped around muscular columns and cords, they are easily removed without damage to the endocardium. On the other hand, genuine thrombi are reddish gray, dry, brittle, opaque, and more or less adherent to the endocardium.

The causes of cardiac thrombosis are practically those of thrombosis of the blood-vessels, the important factors being lesions of the cardiac walls, slowing of the blood-current, and changes in the chemical composition of the blood; thus they are frequently found in hearts the seat of inflammatory, degenerative, and necrotic changes. Acute infectious processes, chronic diseases of the lungs and kidneys, and cachectic states also favor their development. Thrombi are more commonly found in the right chambers of the heart than in the left. In the auricle the favorite seat is the appendix; in the ventricle the neighborhood of the apex. Great variation is observed in the size and shape of thrombi. Some are so small as to be hidden between the muscular columns, while others are large enough to fill an entire chamber. Over focal lesions of the myocardium they may appear as flat, circumscribed deposits, often laminated, and firmly adherent to the heart-wall. In rare instances the mass is more diffuse and is spread over the inner surface of the heart like a false membrane. Among the most familiar examples of cardiac thrombi are the bead-like excrescences or vegetations which spring from the valves in acute endocarditis. Pedunculated thrombi (*Végétations globuleuses* of Laennec) are of common occurrence in the right ventricle. These have often been confounded with genuine polyps. They may be single or multiple. Their surface may be smooth or ribbed, and on section they frequently contain a thick, reddish-brown fluid. Very curious and rare formations are the so-called ball-thrombi. These are spheric masses, loose and freely movable, and varying in size from that of a pea to that of a large walnut. They may be solid throughout or cystic. In nearly all the recorded cases there was mitral stenosis and the thrombus was found in a dilated left auricle.

Secondary changes in thrombi are not infrequent; the most common is liquefaction, the interior of the thrombus being converted into a dark, grumous fluid. Calcification, with the formation of a *cardiolith*, is also possible.

Thrombi may remain indefinitely in the heart without seriously disturbing the circulation, but grave consequences may arise from the obstruction of one of the cardiac orifices or from embolism in an important organ.

Endocarditis.—**Acute Endocarditis.**—It is customary to divide acute endocarditis into simple or benign, and ulcerative or malignant; but no hard and fast line can be drawn between these forms. It was formerly supposed

that only the lesions of ulcerative endocarditis were associated with micro-organisms, and that their presence constituted a point of distinction between this and other varieties ; but subsequent research showed conclusively that the vegetations of the so-called simple endocarditis were rarely free from the same micro-organisms. It is therefore generally conceded that the division of acute endocarditis into benign and malignant is not justified by pathologic differences ; nevertheless, it is convenient, especially from a clinical standpoint, to retain these terms—bearing in mind, however, that they represent only the extremes in a process which manifests all degrees of intensity.

The most common preceding or associated disease in acute endocarditis is acute articular rheumatism. The exact proportion of cases in which these diseases are associated is difficult to determine, as the statistics must rest largely on clinical authority, which is by no means infallible. Bouillaud placed the percentage at 80, and Bamberger at 20. These figures may be regarded as the extremes, and it seems probable that a percentage between 40 and 50 would be not far from correct. While rheumatism so mild as to be readily overlooked may be complicated with endocarditis, yet the latter is more apt to develop when the rheumatism is severe and several joints are involved. Primary attacks of rheumatism are more frequently followed by endocarditis than subsequent attacks. Children with rheumatism are more prone to develop lesions of the heart than are adults. The mitral valve is most frequently affected, and only rarely does the process assume a malignant character. Endocarditis is occasionally met with in the course of tonsillitis, erythema nodosum, peliosis rheumatica, and certain other affections which seem to be related in some way to rheumatism.

Chorea plays a role in the etiology of the disease almost equal in importance to that of rheumatism. Osler found marked vegetations on the valves in 62 of 73 fatal cases of chorea. Endocarditis resulting from this cause is almost always of a benign type.

Septic and pyemic conditions, and the zymotic fevers, especially scarlet fever and croupous pneumonia, are not rarely complicated with acute valvular disease, which may assume either a benign or malignant character.

That endocarditis might occur in the course of gonorrhea was recognized long ago, but only within recent years has it been possible to determine the exact relation of the two affections. Bacteriologic investigations have shown that in some instances the disease was the result of a secondary infection by staphylococci or streptococci which had entered the circulation through the urethral lesion ; in other cases, however, the endocardium seems to have been infected directly by the gonococci themselves. The latter cases were all of a malignant type, and, in 11 of 15 tabulated by Stengel, lesions were found in the aortic valves.

Rokitansky's teaching that there exists between the lesions of the heart and pulmonary tuberculosis a distinct antagonism can no longer be supported. Recent studies have established the fact that cardiovascular disease not only fails to give protection against tuberculosis, but, by producing favorable conditions, actually predisposes to it. Of 500 cases of tuberculosis compiled by Kidd, disease of the heart was found in 27. Of Frommhold's 277 cases of valvular disease, 22 (or 8 per cent.) had phthisis. Potain found pulmonary tuberculosis in 9 of 54 cases of mitral stenosis. Chevers and others have shown that tuberculosis is the most common cause of death in subjects with stenosis of the pulmonary orifice.

When the two diseases are found to be coexistent, it does not follow that the endocarditis is necessarily primary and the phthisis secondary. It has recently been shown that the former may supervene upon the latter. In these cases a careful bacteriologic examination is obviously of great value in determining which affection is primary.

While in most of the cases the inflammation of the valves seems to have been due entirely to a secondary infection, such as may occur toward the close of other wasting diseases, yet instances have been observed in which the bacilli of tuberculosis have been the only micro-organisms detected in the vegetations. The view that these bacilli may hold a causal relationship to the cardiac lesions is supported by investigations recently conducted by Michaelis and Blum. These observers set up aortic incompetence in rabbits by piercing the valves with an instrument introduced through the carotid artery, and subsequently injected tubercle bacilli into the vein of the ear. The animals died of general tuberculosis in from three to six weeks. A postmortem examination showed that the damaged valves were covered with soft vegetations in which tubercle bacilli were found in large numbers.

Traumatism.—Instances in which violent exertion or injuries to the chest have been followed by inflammatory lesions of the heart are sufficient in number to warrant the belief that traumatism itself can be an exciting cause. This belief is further supported by the experiments of Roy and Adami, who demonstrated that the increase of blood-pressure occasioned by applying a ligature lightly to the aorta was soon followed by inflammatory thickening of the valves; and also by the researches of Rosenbach, who showed that endocarditis could be excited by bruising the valves with a wire introduced through the carotid artery. Although it seems well established that a form of inflammation can result from injury, there is no substantial evidence to support the view that a true vegetative endocarditis can be occasioned by this factor alone; that is, without the aid of micro-organisms. On the contrary, the experiments of Wyssokowitsch and others clearly indicate that, when special care is exercised to prevent the entrance of bacteria, mechanic injury to the valves is powerless to produce characteristic vegetations.

Cachectic States.—A benign form of endocarditis sometimes develops toward the close of wasting diseases, such as cancer, phthisis, diabetes, and chronic nephritis. The inflammation in these cases doubtless belongs to that class of terminal infections to which sufferers from chronic diseases so frequently succumb. It is likely that the changes in the blood resulting from disturbed metabolism affect nutrition, and thus render the tissues more vulnerable; moreover, the studies of Flexner indicate that chronic diseases predispose to infection by impairing the bactericidal power normally possessed by the body fluids and cells in a state of health.

Malignant endocarditis is more apt to attack valves which are already the seat of sclerotic changes than valves that are perfectly healthy. The causes of this type of inflammation are the same, in the main, as those of the benign form. It is most frequently met with, however, in association with croupous pneumonia, septic infection, meningitis, or gonorrhea. Rheumatism, chorea, typhoid fever, tuberculosis, influenza, and diphtheria are rare causes. Biggs, Dreschfeld, and others have reported cases in which it developed after traumatism without external wounds. Its connection with gallstones, apart from suppuration, has been noted by Murchison, Netter and

Martha, Jaccoud, Leva, and others. In a few instances it seems to have developed as a primary infection, as no association with an antecedent disease could be traced.

Bacteriology.—Winge¹ in 1869 first demonstrated the presence of bacteria in the vegetations of endocarditis, and Heiberg² in 1872 corroborated this finding; Rosenbach in 1878 first induced the disease experimentally in animals, by injuring the valves by means of a sound passed into the carotid artery. This last observer also found in the valvular lesions the micro-organisms that had entered the circulation during the operation, and concluded that their presence was in part responsible for the growth of the vegetations, as the latter could not be attributed solely to the effects of the mechanic injury. Later investigators (Ribbert, Rodet, Dreschfeld, Roux, Josseraut, Michaelis, and others) showed that the disease could be induced simply by the introduction of various species of bacteria into the circulation without the aid of any previous injury or disease of the valves. Although both experimental and pathologic studies indicate that micro-organisms are the chief factor in the development of acute endocarditis, it is evident that no one species is to be held accountable for its production.

Of 29 cases studied by Weichselbaum, 7 showed the *Micrococcus lanceolatus*, 6 the streptococcus, 2 the *Staphylococcus pyogenes aureus*, 6 unusual bacteria, and in 8 the bacteriologic examination gave negative results. Of 19 cases studied by Stokes and Wright,³ 9 were associated with *Micrococcus lanceolatus*, 2 with streptococcus, 2 with *Staphylococcus pyogenes aureus*, and in 6 the results were inconclusive. In Flexner's 34 cases⁴ the *Micrococcus lanceolatus* and the streptococcus were found each 12 times, and the staphylococcus 3 times. It is therefore apparent that the chief offenders are the *Micrococcus lanceolatus*, the streptococcus, and the *Staphylococcus pyogenes aureus*. It is probable, however, that the above figures do not represent the exact etiologic relation of the various species of bacteria to acute endocarditis in all of its degrees of intensity, since in the main they are based upon the study of the infection as it develops in the course of grave or fatal diseases. Among other micro-organisms which have been found in the diseased valves may be mentioned the gonococcus, bacillus of tuberculosis, bacillus of diphtheria, *Bacillus coli communis*, *Bacillus pyocyaneus*, and bacillus of influenza.

In some instances the disease is apparently the result of a mixed infection, since two or more species of bacteria are found in the same lesions.

While it has been shown that the introduction of bacterial toxins into the circulation is capable of exciting various degenerative changes in the heart and blood-vessels, investigators have thus far failed to induce a true vegetative endocarditis without the presence of the bacteria themselves.

Morbid Anatomy.—Acute endocarditis much more frequently attacks the valves of the heart than the lining of the cavities. The mitral valves are involved first in frequency, then the aortic, tricuspid, and pulmonary valves. Lesions of the right side of the heart, acquired in extra-uterine life, are not so rare as formerly supposed. Sansom states, and Bramwell agrees with him, that the right side of the heart is affected in at least 50 per cent. of all acute inflammations of the endocardium and in almost every case of severe

¹ Nordiskt medicinskt Arkiv, 1870.

² Boston Med. and Surg. Jour., Mar. 21, 1895.

³ Jour. of Exp. Med., 1, p. 559, 1896.

⁴ Virchow's Archiv, lvi., 1872.

endopericarditis. These authors express the belief that the relative infrequency of chronic lesions of the tricuspid and pulmonary valves is due to the fact that resolution is more often effected on the right side of the heart, since its valves are subjected to less strain.

In severe forms of endocarditis it is not uncommon to find other parts of the endocardium involved, especially the chordæ tendineæ, the left ventricular aspect of the septum, and the posterior wall of the left auricle. The valves are generally first affected on the aspect facing the direct blood-current; that is, on the auricular surface in the case of the mitral valves, and on the ventricular surface in the case of the aortic valves. In neither are the lesions at the very edge, but along the line of maximum contact where there is greatest friction, and which is about 2 mm. from the free margin. The affected regions, which are at first only slightly rough and opaque, soon become studded with chains of delicate excrescences or vegetations. The latter are usually 2 or 3 mm. in diameter, and are lightly attached to the valves by slender pedicles. When recent, they are friable, grayish-pink in color, and almost transparent; when old, they are firm, white, and opaque. The microscopic appearances also vary with age. A section of the affected valve in the early stage of the process shows a superficial area of necrosis, void of nuclei, and overlaid with a fibrinous deposit, granular or fibrillar, enclosing a greater or less number of white and red blood-cells. When the section is properly stained, colonies of bacteria are frequently detected within the thrombus or in the upper layers of the endocardium. In the later stages, round-cell infiltration and proliferation of the connective-tissue elements are visible in the adjacent tissue. With the growth of the granulations beyond the surface of the valve, the original thrombus disintegrates and ultimately disappears. Not rarely, however, a secondary coagulum is subsequently formed over the inflammatory proliferations.

The term *warty* or *verruose endocarditis* is used to designate a less severe form of infection, in which the necrotic process is limited and proliferation is more extensive than is required for the purpose of repair. When, however, necrosis is the prominent factor, and the reparative process is subordinate, the endocarditis is termed *ulcerative* or *malignant*. In such cases there is a marked loss of substance from the separation of the dead tissue and superimposed thrombi.

In the present state of our knowledge, it is impossible to state with absolute certainty the exact sequence of events that takes place in infective endocarditis; but it is probable that the first changes are of degenerative or necrotic character, that these are followed by the deposition of fibrin from the blood, and that subsequently, as a final reaction, a true inflammatory process is established, manifested by cellular exudation and proliferation.

Terminations.—In rare instances the vegetations undergo molecular disintegration or are slowly absorbed, leaving the valves so slightly damaged that their functions remain unimpaired. Usually, however, the thrombotic deposit is gradually replaced by fibrous tissue, which not only thickens the valves, but, by contracting, so shortens and distorts them that they are rendered, in one instance, obstructive to the onward flow of blood, and, in another, incompetent to close the orifice over which they preside. Finally the process is completed by the valve becoming the seat of calcareous infiltration and by the new fibrous tissue undergoing fatty or hyaline degeneration. Sometimes remnants of thrombi remain permanently attached,

undergo calcification, and thus still further interfere with the functions of the valves.

The detachment of a thrombus or the separation of a fragment of necrotic tissue is a common cause of embolism, the obstruction most frequently occurring in the brain, spleen, kidney, or arteries of the extremities.

Ulcerative endocarditis sometimes leads to valvular aneurysm or even to rupture of the valves or chordæ tendineæ; or, if it involves the mural endocardium, it may give rise to suppurative myocarditis or pericarditis, or it may excite aneurysm or rupture of the cardiac walls.

Associated Lesions.—The heart-muscle is probably more or less involved in every case of acute endocarditis. Romberg has emphasized the fact that the symptoms of acute endocarditis are not so much due to the valvular

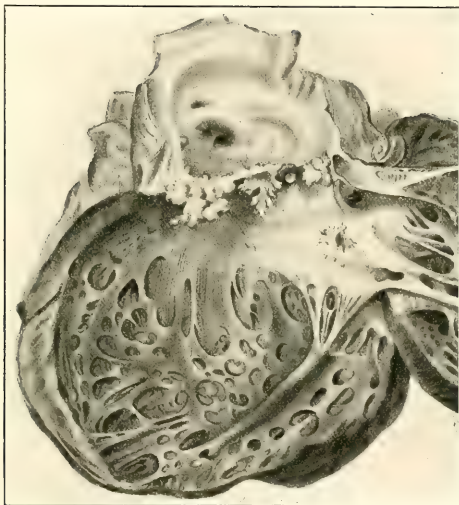


FIG. 170.—Acute ulcerative endocarditis.

defects as to the associated lesions in the myocardium. In two cases of acute valvular disease of rheumatic origin, he found, in addition to some parenchymatous degeneration, acute interstitial myocarditis and hyaline thrombosis of many small blood-vessels. These lesions, particularly the occlusion of the small arteries, must contribute considerably to the disturbance of the heart's action in acute inflammation of the valves.

Pericarditis is likewise a frequent attendant upon acute endocarditis, particularly when the latter occurs in childhood. It was present in 34 of 161 cases of acute valvular disease observed by Sibson. Sturges states that of 100 fatal cases of heart disease occurring at the Children's Hospital within a period of ten years, of which 54 were of rheumatic origin, and 46 due to other causes, in 6 only was there no evidence of pericarditis.

Chronic Endocarditis.—Chronic endocarditis is often the sequence of a

previous acute attack. Not infrequently, however, the disease develops insidiously as the result of the long-continued action of some irritant which is apparently contained in the blood; thus it may be intimately associated with gout, chronic alcoholism, chronic lead poisoning, syphilis, or diabetes. Prolonged immoderate exertion is an important factor. In old age the disease often develops coincidently with sclerosis of the vessels, the two affections having a common etiology.

Morbid Anatomy.—The affected parts are slightly thickened, dull, and opaque. Sometimes along the edge of the valves there are slight nodular elevations, presenting a grayish-red appearance. Much more important is the puckering brought about by the contraction of the newly formed tissue; it is this which so seriously impairs the function of the valves.

Shortening of the chordæ tendineæ, which often share in the inflammatory process, also serves to restrict the movements of the auriculoventricular valves. Frequently necrotic and degenerative changes supervene and bring about softening and disintegration. The dead tissue may then become firm and opaque from the deposition of lime salts, or it may become detached and leave behind a shallow excavation, to which the term atheromatous ulcer has been applied. Surrounding the necrotic focus there is always evidence of an acute inflammatory process, and doubtless the latter is the important factor in causing the cohesion of the valves which is sometimes observed. Valves the seat of chronic inflammation frequently become infected, in which case the vegetations characteristic of acute endocarditis appear.

Associated Conditions.—The stenosis or insufficiency of the valves resulting from chronic endocarditis necessarily throws an extra amount of work upon certain parts of the heart, the effect of which is to induce hypertrophy or dilatation, one or the other predominating according to the nature and gravity of the lesion and the state of the cardiac muscle. An enlargement which is just sufficient to accomplish the additional work is termed a compensatory hypertrophy. So long as the latter continues the patient experiences little or no discomfort, since the heart, notwithstanding the valvular lesion, is able to supply the arterial system with its normal quota of blood. When, however, the heart is unable to meet the increased requirements, dilatation ensues and compensation is said to be lost. Under these circumstances the veins become surcharged with blood and the arteries depleted, a condition which immediately calls forth a train of distressing symptoms.

Changes in the myocardium are rarely absent in chronic endocarditis; and, as a rule, more depends upon the character, extent, and location of these changes than upon the valvular defect itself. The lesions of the heart-muscle, which comprise hyperplasia of the connective tissue and various degenerations of the parenchyma, may be related in several ways to the valvular disease. In the first place, they often develop simultaneously with endocarditis as the result of one and the same cause. Again, they may be due to sclerosis of the coronary arteries which has developed at a later period than the endocarditis and from causes in no way related to the latter. Thus compensatory hypertrophy is often well maintained until old age itself effects sclerotic change in the arteries of the heart. In some cases the myocardial lesions, at least in part, are directly dependent upon the valvular affection. Thus in mitral disease Banti has found what he terms venous cirrhosis in contradistinction to arterial cirrhosis. The coronary veins and their branches are dilated, the intermuscular tissue is overgrown, and the

muscle-fibers are vacuolated, degenerated, and atrophied. This condition appears to be dependent upon imperfect emptying of the coronary vein into the right auricle. In aortic disease the valvular defect may seriously interfere with the filling of the coronary arteries, and in consequence there may be a secondary degeneration in the myocardium.

Disease of the Aortic Valve.—Disease of the aortic valve is conventionally divided into stenosis and insufficiency; but, as a matter of fact, these two conditions are often associated, the retraction and curling of the segments occasioned by sclerotic endocarditis giving rise to both incompetence and obstruction. Pure aortic stenosis is rare; it is usually due either to cohesion of the valve-segments or to constriction of the aortic ring. Aortic insufficiency may result from sclerotic endocarditis or actual rupture of one of the cusps. Rarely relative insufficiency may arise from the inability of normal valves to close an orifice which has been unduly distended by aneurysm of the ascending aorta or extreme dilatation of the left ventricle.

In aortic stenosis the increased resistance offered to the expulsion of blood from the left ventricle results in hypertrophy of that chamber; but, as there is little tendency to dilatation, the enlargement is rarely so extreme as in aortic regurgitation. Ultimately, however, the ventricles may yield to the severe strain, and, in so doing, occasion insufficiency of the mitral valves.

In aortic regurgitation the increased intraventricular pressure which follows the recoil of blood from the aorta in each diastole causes a permanent dilatation of the left ventricle, while the increased labor entailed by expelling an abnormal quantity of blood in each systole favors the development of a compensatory hypertrophy; as a consequence, the heart attains a larger bulk than in any other affection. Later sequences are stretching of the mitral ring, relative insufficiency of the mitral valve, enlargement of the left auricle, and finally dilatation of the right ventricle and relative insufficiency of the tricuspid valve.

Disease of the Mitral Valve.—In lesions of the mitral valve, as in those of the aortic valve, stenosis and insufficiency are frequently associated. Very often, however, one or the other condition predominates. Mitral stenosis is nearly always the result of a prenatal or a postnatal endocarditis. All degrees of obstruction are encountered. In severe cases fusion of the segments and constriction of the parts reduce the orifice to a narrow slit—the “buttonhole” form of mitral stenosis. More rarely the valve is converted into a smooth membranous cone, with its smaller aperture directed toward the apex of the heart—the “funnel-shaped” form of mitral stenosis. The changes in the heart resulting from mitral stenosis involve chiefly the left auricle and the right ventricle. On account of the hindrance to the outflow of blood, the left auricle first becomes dilated and then hypertrophied. In some cases the auricular walls attain a thickness of from $\frac{1}{8}$ to $\frac{1}{4}$ inch. The appendix of the auricle is especially affected; it may become enormously distended and elongated. Moxon records a case in which it measured $2\frac{3}{4}$ inches in length.

Thrombi are frequently found in the interior of the left auricle. They may be attached to the endocardium by slender pedicles so as to resemble polyps, or they may be entirely free and thus assume a globular shape. They may be so situated as to offer an additional impediment to the passage

of blood through the mitral orifice. Osler has reported a case in which sudden death resulted from the occlusion of a funnel-shaped mitral orifice by a ball-thrombus.

An increased tension in the pulmonary circulation, which is present throughout in mitral stenosis and which reaches its maximum when the auricular hypertrophy ceases to be compensatory, leads to hypertrophy and eventually to dilatation of the right ventricle. Marked dilatation of the right ventricle may finally render the tricuspid valve incompetent. The left ventricle is not enlarged, being usually normal in appearance; occasionally, however, it is unnaturally small.

Mitral regurgitation is the commonest form of valvular disease. It may be due to chronic endocarditis, resulting in curling and retraction of the mitral segments or in shortening and stiffening of the chordæ tendineæ. The most common cause is dilatation of the left ventricle or relaxation of its muscular walls, whereby the valve-segments are rendered incompetent to

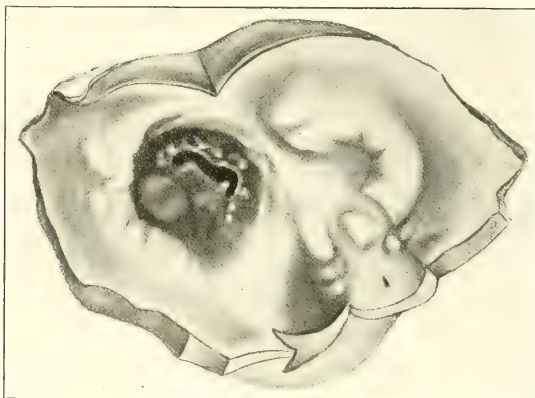


FIG. 171.—Buttonhole mitral valve (Ashton).

close the orifice during systole. Occasionally the disease results from rupture of the valve-curtains or the chordæ tendineæ.

The first effects of mitral regurgitation are enlargement of the left auricle and left ventricle. The former is due to the influx of blood from two sources, from the lungs and the left ventricle; the latter is due to the large amount of blood received from the auricle during diastole. As in mitral stenosis, the increased tension in the pulmonary circulation soon brings about hypertrophy and dilatation of the right ventricle, and eventually tricuspid insufficiency and dilatation of the right auricle may follow.

Disease of the Tricuspid Valve.—Tricuspid stenosis may be congenital or acquired. When congenital, it may be due to intra-uterine endocarditis or a vice of development; when acquired, the disease is always the result of endocarditis which is usually of rheumatic origin. In a series of 154 cases, comprising 114 collected by Leudet and 40 by Herrick,¹ 114 were

¹ *Boston Med. and Surg. Journ.*, March 18, 1897.

females, 32 were males, and in 8 the sex was not stated. In 84 of these cases the age was between twenty and forty years. In only 12 instances was the tricuspid valve alone involved. It is noteworthy that in 138 cases, or nearly 90 per cent., mitral stenosis coexisted. In 39 cases both the aortic and mitral valves were involved. In no case, however, as Ashton points out, were tricuspid and aortic stenosis combined, unless there existed also mitral stenosis. Tricuspid stenoses probably always brings about marked enlargement of the right auricle; but, as other valves are usually affected, it is common to find a general enlargement of the heart.

Tricuspid regurgitation is usually secondary to the lesions of the mitral valve or to diseases of the lung which obstruct the pulmonary circulation, such as emphysema, chronic bronchitis, and fibroid pneumonia. In these cases the valve-segments may remain normal, the insufficiency being relative and entirely dependent upon the dilatation of the right ventricle and the distention of the tricuspid orifice; or the valve-segments themselves may slowly undergo sclerotic and degenerative changes, as a result of the increased tension to which they are subjected. Occasionally the disease develops independently as the result of acute or chronic endocarditis. Tricuspid regurgitation affects the right side of the heart, as mitral regurgitation affects the left side. The right auricle and the right ventricle are usually considerably enlarged.

Disease of the Pulmonary Valve.—Stenosis of the pulmonary valve is almost invariably of congenital origin. It is often associated with other anomalies of development, such as a pervious state of the ductus arteriosus and defects in the cardiac septa. In rare instances the disease is acquired in the course of acute rheumatism or some other infection. Chevers and others have shown that pulmonary tuberculosis is an extremely common cause of death in subjects with congenital pulmonary stenosis.

Pulmonary insufficiency is the rarest form of valvular disease. Pitt states that only 17 cases have been noted in the postmortem room at Guy's Hospital, out of 11,000 examinations, during a period of twenty-three years. He has collected from various sources 99 cases, all of which were confirmed by necropsy. The affection may be congenital or acquired. The latter may result from infectious endocarditis or dilatation of the pulmonary artery. Occasionally a thoracic aneurysm, by pressing on the pulmonary artery near the valves, causes an adhesive inflammation which results in insufficiency.

THE ARTERIES.

Retrogressive Changes.—**Hypoplasia.**—In certain cases of chlorosis the walls of the large arteries are unnaturally thin and elastic and the lumen of the aorta is no larger than that of a child's. Some aneurysms seem to be dependent upon a defective development of the media. Hypoplasia of the blood-vessels has also been observed in hemophilia.

Atrophy of the arterial walls may occur as the result of wasting diseases. In atrophy of individual organs the blood-vessels may share in the process. As a rule, the loss of substance is intimately associated with changes of an inflammatory or degenerative character.

Fatty changes are common. They may be confined to the endothelial cells of the intima, but in some instances the deeper layers of the intima and the muscle-cells of the media are also affected. They occur in association

with other morbid changes in arteriosclerosis; as an independent affection they may result from the action of various toxic substances present in the blood. To the naked eye the affected areas are whitish and opaque; microscopically the cells are granular and filled with minute oil globules. Fatty changes of this kind may lead to rupture of the vessel, or they may be followed by calcareous infiltration.

Calcareous infiltration is generally met with as an accompaniment of fatty degeneration or arteriosclerosis. The intima and the media are the parts affected. In extensive calcification of the media the artery may appear as a rigid tube.

Amyloid degeneration of the organs is first manifest in the arteries. In small vessels the degeneration affects all the coats; in large vessels the intima is chiefly involved.

Hyaline degeneration is frequently observed in the blood-vessels of old persons; it is an important factor in arteriosclerosis; it often attacks the arterioles and capillaries in infective processes and intoxications; and finally it is often well marked in the arteries of certain sarcomas (cylindromas). Small vessels may present a beaded appearance from the irregular deposit beneath the endothelium of a clear, homogeneous, refractive substance, which reacts well with Weigert's fibrin-stain. In the large vessels the walls are more uniformly affected; the process, however, is most marked in the intima and connective tissue of the media.

Hypertrophy.—Hypertrophy of the arteries results from increased blood-pressure, and is seen in the establishment of a collateral circulation when an important arterial trunk has been occluded.

Inflammations.—Acute Arteritis.—Acute inflammation of the arteries may result from external injury, extension of disease from adjacent structures, or from certain general infections or intoxications. Recent bacteriologic investigations have thrown much light upon the pathology of acute arteritis occurring in the course of infective processes. Boinet and Romary were able to excite acute arteritis by injecting into the circulation various pathogenic bacteria, without having previously injured the intima. They further demonstrated that the bacteria themselves were not necessarily the cause of the inflammation, since the latter could be excited by the injection of bacterial toxins alone. It is conceivable that the noxious agent may reach the intima through one of three channels—the main blood-stream, the vasa vasorum, or the lymphatics. Careful bacteriologic and histologic studies indicate, however, that in most instances the irritant is carried directly to the intima by the blood in the main stream.

The macroscopic appearances vary considerably according to the cause of the inflammation. The intima is usually somewhat reddened by liberated blood-pigment. More or less circumscribed, slightly elevated gelatinous plaques are frequently found projecting from the surface into the lumen of the vessel. More rarely thrombotic excrescences are observed, similar in all respects to the vegetations appearing on the valves of the heart in acute endocarditis.

Sometimes, but not so often as in phlebitis, the vessel is occluded at the seat of the lesion by an infective thrombus. To this group of cases the term *thrombo-arteritis* has been applied. Various opinions have been held as to the relation existing between the thrombus and the arteritis. Hunter taught that the inflammatory changes in the vessels were primarily effected, and

that the formation of the thrombus was a secondary event. On the other hand, Virchow and his followers have contended that the arteritis, instead of being the cause, is nearly always the result of the infective thrombus. Bacteriologic studies, however, do not support Virchow's contention, but indicate that in the majority of cases of infective arteritis the thrombosis is a secondary process. It has not been proved that the usual order of events may not be reversed in some instances, as is the case in that form of arteritis occurring in pyemia, in which the lodgement of a septic embolus is undoubtedly the primary factor.

Microscopically all the coats are involved, but not to the same extent. The intima and media sustain the brunt of the attack; and one of these tunics is affected more or less than the other, according as the invasion has started from without or from within the vessel. Nuclear fragmentation and necrosis are more or less marked in the intima. Beneath the endothelium there is an accumulation of spindle-cells or stellate cells, which are probably derived from the fixed connective-tissue cells or from the endothelial cells. The vasa vasorum are congested and surrounded by dense aggregations of small round cells.

Slight attacks of acute arteritis, no doubt, frequently end in complete resolution. That the lesions excited by acute infective processes may in some instances ultimately lead to arteriosclerosis is not improbable.

Acute aneurysmal dilatation or actual rupture of the artery sometimes occurs, when the process is localized and intense. Thrombo-arteritis not infrequently terminates in organization of the thrombus. When this occurs the fibrinous plug is gradually absorbed and replaced by a new formation of connective tissue, which springs from the coats of the artery. The ultimate result of this metamorphosis may be partial obliteration of the lumen of the vessel by fibrous bands or the complete conversion of the vessel into an impervious fibrous cord (*proliferative arteritis* or *endarteritis obliterans*).

Acute Suppurative Arteritis.—Acute suppurative arteritis may result from the extension of a septic inflammatory process from the neighboring tissues to the vessel-walls, or from the presence in the vessel of an embolus or thrombus containing pyogenic organisms. The microscopic changes consist in extensive necrosis of the tissues at the seat of the invasion and an abundant infiltration with round cells, the lesions being more marked in the adventitia or in the intima, according as the process extended from without or from within the vessel. In large arteries yellowish-white accumulations of pus may be visible to the unaided eye. Acute aneurysmal dilatation or rupture of the vessel is a possible result of the disease.

Arteriosclerosis.—(Atheroma; arteriocapillary fibrosis; chronic end-arteritis; arteritis deformans).

Definition.—A circumscribed or diffuse thickening of the arterial walls, especially of the intima, secondary to certain inflammatory or degenerative changes in the media.

The term arteriocapillary fibrosis, introduced by Gull and Sutton, is sometimes employed to designate the process when it involves the capillaries as well as the arteries. Thoma has suggested the name angiosclerosis for the condition when it affects the whole vascular system. When the disease affects the aorta and the large arteries and the degenerative changes are marked, it is by some spoken of as atheroma.

Etiology.—While arteriosclerosis sometimes occurs in persons quite

young, it is chiefly met with in later life; indeed, in many instances it is to be regarded as a natural accompaniment of senescence.

The causes which favor the early development of the disease operate through the blood, either by increasing its distensive force or by effecting changes in its composition. That mechanic strain itself is an important etiologic factor is confirmed by the fact that blood-vessels and parts of blood-vessels that are most subjected to the insults of the blood-stream are the earliest and most severely affected, and also by the fact that disease develops so frequently and so soon in persons who are engaged in occupations that require continued muscular exertion. Infections and intoxications which load the blood with noxious materials are common causes of arterial sclerosis; thus, syphilis, gout, rheumatism, Bright's disease, alcoholism, and chronic lead poisoning frequently excite it. In these cases the morbid agent may act in two ways: first, directly, by attacking the vessel-walls through the



FIG. 172.—Normal left carotid artery in cross-section: *a*, elastica interna; *b*, media; *c*, elastica externa; *d*, adventitia; *e*, vasa vasorum. Staining of the elastic fibers by Weigert's method (Malkoff).

vasa vasorum; and secondly, indirectly, by increasing the peripheral resistance, and in consequence raising the arterial pressure. It is highly probable that acute infectious diseases often produce, as in the case of chronic interstitial myocarditis, changes in the arteries which become the foundation of subsequent fibrosis. Pale-red gelatinous plaques have frequently been observed on the inner surface of the aorta after death from such diseases as erysipelas, acute rheumatism, and diphtheria. Hollis has cited the case of a child dead four days after an extensive burn, in whose aorta there were found streaks of early and evidently recent sclerotic changes. Microscopic study of the smaller arteries after infectious processes has revealed swelling and fragmentation of the endothelial cells, hyaline degeneration of the muscularis, and an accumulation of leukocytes in and about the vasa vasorum and in the perivascular lymph-spaces, lesions which seem quite capable of leading up to chronic endarteritis.

Morbid Anatomy.—Certain arteries show a special predisposition to sclerosis; thus, the aorta is most frequently, and usually most extensively, diseased. After the aorta, the vessels most commonly affected are the splenic, iliac, femoral, anterior tibial, coronary, cerebral, and brachial. On the other hand, sclerotic changes are rarely observed in the gastric, mesenteric, and hepatic arteries.

Two varieties of arteriosclerosis may be recognized: the circumscribed or nodular, and the diffuse.

Circumscribed or Nodular Form.—The macroscopic appearances vary according to the stage of the process. When the disease is of recent origin, an examination of the inner surface of the aorta reveals the presence of irregular plaques, having a translucent and somewhat gelatinous appearance. At a later period, these are firm and almost cartilaginous. When old, they are whitish or yellowish in color, and opaque from calcification and degeneration of their deeper layers. Extreme calcification leads to the formation of hard, brittle plates, which project into the lumen of the vessel and favor the deposition of fibrin. Not infrequently the necrotic tissue disintegrates and is converted into a soft, fatty detritus, which bursts through the superficial layers of the intima into the lumen of the vessel, thereby creating a so-called atheromatous ulcer. In many instances every stage of the process is represented within a limited area of the vessel; thus, fibrous nodules, calcareous plates, and atheromatous ulcers may be found side by side.

A microscopic examination of a sclerotic nodule shows that all three coats of the artery are more or less affected. The changes in the intima, in the first instance, consist in a marked proliferation of the subendothelial connective tissue. The endothelial lining itself, though pushed forward into the lumen of the vessel, often remains intact until the process is far advanced. The fusiform or stellate connective-tissue cells constituting the hyperplasia are at first well defined; but eventually the deeper ones, as the result of retrograde changes, chiefly hyaline and fatty degeneration, undergo disintegration and are replaced by oil-drops, crystals of cholesterol, fatty acids, and molecular débris. As an evidence of reaction, a round-cell infiltration is often observed in the vicinity of the necrotic areas. The media shows a distinct loss of tissue at points corresponding to the hyperplasia in the intima. The remaining muscle-fibers are the seat of hyaline and fatty degeneration; the elastic fibers are sometimes torn, and a round-cell infiltration is often present about the vasa vasorum. The adventitia generally shows a hyperplasia of the fibrous elements and a cellular infiltration.

Important changes take place in the *elastic tissue*. These are both degenerative and proliferative. The degenerative change begins early, usually in the inner layer of the media—the elastic lamellæ become thinner, their affinity for certain stains becomes altered, and finally they break down. The new formation of fibers is especially marked in the intima. The new elastic tissue is less resistant than the old, and yields readily to softening processes. Fig. 172 represents a normal artery stained to show the elastic fibers. In Fig. 173 the effect of the atheromatous process on the intima and media, including the elastic fibers, is well shown.

The Diffuse Form.—In this form of arteriosclerosis the process is more uniform, and often involves, in addition to the aorta and its branches, the smaller arteries, especially those of the kidney, brain, and heart. This form is usually observed in middle-aged men, and is very common in the negro

race. It is often associated with the nodular form in the large arteries. The intima is usually smooth; but, beneath the endothelial lining, white opaque patches are, as a rule, easily recognized. Microscopically the changes are similar to those observed in the nodular form. In the intima there is a marked hyperplasia of the subendothelial connective tissue; the latter, however, from having undergone hyaline degeneration, may appear almost structureless. In the smallest arteries the elastic lamina is often entirely wanting or represented only by a few disjointed fragments. The muscular fibers in the media are atrophied and the seat of fatty degeneration. In many of the arterioles, especially those of the kidney, all semblance to the normal structures is lost, the coats of the vessel being converted into a homogeneous hyaline tissue.

Pathogenesis.—In regard to the manner in which the changes peculiar to sclerosis are effected in the arterial walls, there has been considerable discussion. The idea originally entertained was that the lesions in the intima were primary and were the result of an inflammatory process excited by the direct action of an irritant conveyed to the part by the blood. At the present

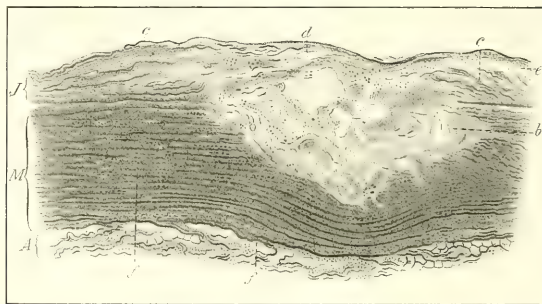


FIG. 173.—An atheromatous patch in the abdominal aorta which has not yet broken through: *J*, intima; *M*, media; *A*, adventitia; *b*, atheromatous necrotic focus in the intima and media; *c*, elastic fibers of the intima; *d*, elastic fibers which have persisted between the necrotic focus and the endothelial layer; *e*, thickened endothelium; *f*, infiltration of the media with small cells (Dmitrijeff).

time this view has few supporters; most authorities now agree with Rokitsansky and Thoma in regarding the thickening of the intima as secondary to and dependent upon the degenerative changes in the media. According to Thoma, the thickening of the arterial walls, especially of the intima, is compensatory and designed to offset, in a measure, the loss of tissue sustained by the media.

To support this view and to prove that the sclerotic nodules, found post-mortem in the large arteries, simply fill up, during life, depressions produced by the weakening of the media, Thoma showed that casts made by forcing paraffin into the aorta and large arteries, under a pressure equal to that normally exerted by the blood, came out quite smooth and did not present the indentation which they would have shown had not the overgrowth of tissue in the intima closely corresponded to the loss of substance in the media.

While it is generally conceded that the thickening of the arterial coats is the result of the weakening of the media, the immediate cause of the

latter is a matter in which opinion is still divided. Köster believes that the primary lesion is an infiltration of the media; that is, a mesarteritis, and that the conversion of the cellular infiltration into fibrous tissue causes constriction of the vasa vasorum and thus induces secondary nutritive changes. According to Mott, degeneration of the media is often primarily due to obliteration or obstruction of the vasa vasorum and consequent defective nutrition of the muscular fibers. The causes of arteriosclerosis are so various that it is not unreasonable to suppose that the manner of its development may vary in different cases. It is not unlikely that the arteriosclerosis following certain infectious processes may originate in a mesarteritis or periarteritis, while that due to old age may result directly from a loss of elasticity in the media. High arterial tension may act also by first impairing the tonus of the muscularis, and thereby exciting a compensatory hyperplasia of the intima.

Tuberculous Arteritis.—Tuberculous arteritis may result from the direct extension of a tuberculous process originating outside of the vessel, from the presence within the vessel of an infected embolus, or from the

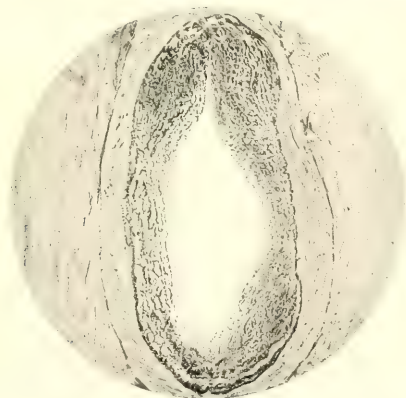


FIG. 174.—A branch of the coronary artery, showing syphilitic endarteritis. The new growth of the intima is almost entirely made up of elastic fibers which are in immediate relation with the thickened fenestrated membrane. Weigert's stain. $\times 50$ (Abramow).

direct implantation on the vessel-wall of bacilli contained in the blood. The disease most commonly affects the small arteries, especially those of the brain, lungs, and kidneys. The process is manifested by the presence of discrete tubercles in the adventitia or by thickening of the vessel-wall from a diffuse cellular infiltration. The latter consists of round cells, fusiform or stellate epithelioid cells, and a few giant cells. Partial or complete obliteration of the lumen of the vessel may result from marked infiltration and proliferation in the intima or from thrombosis. The new formation sometimes undergoes cheesy necrosis; and this, in the absence of thrombosis, may occasion aneurysmal dilatation or rupture of the vessel. In other instances the process culminates in a simple fibrous hyperplasia of the adventitia and intima, the lumen of the vessel being partially or completely occluded.

Tuberculosis of the large arteries is rare. Blumer¹ has reported 2 cases of tuberculous aortitis and has collected 8 others. In 7 of these the tubercle was probably due to direct implantation of infective material on the vessel-wall, and in 3 the tuberculous process originated outside of the vessel, either in consolidated lung or adherent lymph-gland.

Syphilitic Arteritis.—Syphilitic arteritis may result from the spread of a local syphilitic affection or from the direct action of the toxin upon the blood-vessel walls. The cerebral arteries, coronary arteries, and aorta are the vessels most frequently involved. While the lesions are often those of arteriosclerosis, there is a special form of syphilitic arteritis in which the chief feature is a marked hyperplasia of the adventitia and intima, which obliterates partially or completely the lumen of the vessel. This hyperplasia consists, according to its age, of epithelioid cells and round cells—in the really typical instances arranged to form gummas in the vessel-wall, especially the adventitia—or of fully developed fibrous tissue. In some cases all three coats are involved. When the process is arrested, an attempt at regeneration is apt to take place, with new formation of elastic fibers in the intima from the fenestrated membrane.

There is much less tendency to degeneration in syphilitic than in other forms of chronic arteritis. In the cerebral arteries the process sometimes assumes a nodular form, owing to cellular accumulations and gummatous formations in the adventitia.

Periarteritis Nodosa.—Periarteritis nodosa is a rare form of arterial disease characterized by the appearance, on the walls of the vessel, of multiple nodules varying in size from that of a millet seed to that of a pea. Microscopic examination of these nodules reveals marked cellular infiltration of all the coats of the artery and more or less extensive degenerative and necrotic changes. Thrombosis and acute aneurysmal dilatation frequently accompany the process. The cause of this disease is not apparent; but the sudden onset, acute course, and muscular atrophy suggest the operation of some infective agent. The vessels of the brain usually escape, the change being most marked in the peripheral arteries and in those of the heart, liver, spleen, mesentery, and kidneys. Periarteritis nodosa is interpreted by Eppinger as a form of congenital aneurysm, dependent upon defective development of the elastic coat and characterized by multiple aneurysmal dilations in many of the medium-sized arteries; but there is no good evidence in favor of this view.

Aneurysm.—An aneurysm is a more or less circumscribed dilatation of an artery. When the dilatation involves the whole contour of the vessel, it is termed a *fusiform aneurysm*. When the bulging involves only one side of the vessel and communicates with the latter by a relatively small orifice, it is termed a *saccular aneurysm*. The term *cirsoid aneurysm* has been applied to a form in which the vessel is not only dilated, but also tortuous and elongated. Rupture of the intima, with the passage of blood between the outer tunics of the vessel, constitutes a *dissecting aneurysm*. The blood may ultimately escape into the surrounding tissues, or it may return to the lumen of the vessel through another opening in the intima. A condition in which the blood has burst through all the coats of the vessel and has, out of the surrounding tissues, formed for itself an adventitious sac, is termed a *false aneurysm*. As varieties of the latter may be mentioned: (a) *Aneu-*

¹ *Am. Jour. Med. Sci.*, Jan., 1899.

rysmal varix, a condition in which both an artery and a vein have been wounded, and the blood from the former flows directly into the latter; and (b) *varicose aneurysm*, a condition in which an artery and a vein communicate indirectly through an intermediate adventitious sac.

Etiology.—In the vast majority of cases, aneurysm results from degenerative changes in the vessels, excited by syphilis, alcoholism, gout, lead poisoning, or immoderate physical exertion. In at least 50 per cent. of the cases, a history of syphilis is obtainable. Age, sex, and occupation are important factors. Of 173 cases of aortic aneurysm tabulated by Browne, 113 occurred between the ages of thirty-five and fifty-five years. These statistics coincide closely with those recorded by Crisp, who analyzed 551 cases and found 398 between the ages of thirty and fifty years. Between 80 and 90 per cent. of all cases occur in males. Persons engaged in occupations which require violent muscular exertion are more liable to aneurysm than those who follow more quiet pursuits.

In some instances the disease apparently depends upon a defective development of the arteries. This is probably the explanation of the multiple aneurysms which are occasionally encountered in early life or even at birth. Virchow and Dickinson have called attention to the association, in some cases, of aneurysm and arterial hypoplasia. In the smaller arteries, dilatation may follow an eroding process which has invaded the walls of the vessel from without. Multiple aneurysms from this cause are frequently found in the lungs in advanced phthisis. Embolism is another cause of aneurysm in the smaller arteries. The embolus may be infectious and excite inflammation and degeneration of the vessel-walls at the seat of the occlusion, or it may be a calcareous plate; in which case, the breaking of the walls may have its origin in mechanic injury. The occurrence of multiple aneurysms in malignant endocarditis as the result of an acute mycotic arteritis was pointed out by Osler.

In the horse, aneurysm of the mesenteric arteries is not infrequently due to the *Strongylus armatus*. The larvæ of these worms bore into the coats of the vessel and bring about necrotic processes which culminate in aneurysmal dilatation.

Seats.—The aorta is by far the most common seat of aneurysm. After the aorta, the arteries most frequently affected, in order of incidence, are the popliteal, femoral, carotid, subclavian, axillary, and innominate. Browne states that there were 631 cases of aneurysm treated in St. Bartholomew's Hospital between 1867 and 1897. In 468 of these the disease affected the aorta, in 80 the popliteal, in 21 the femoral, in 14 the subclavian, in 8 the innominate, in 8 the carotid, and in 6 the external iliac. In 332 cases exclusive of aortic aneurysms, analyzed by Agnew, 145 were popliteal, 88 femoral, 21 carotid, 15 axillary, 13 innominate, 12 brachial, 12 subclavian, 9 intra-orbital, 3 temporal, 3 gluteal, and 1 subscapular.

Morbid Anatomy.—Aneurysms vary considerably in size; some, like those met with in the brain, may be almost microscopic, while those affecting the aorta may reach the dimensions of a child's head. The most common varieties are the saccular and fusiform.

When the aneurysm is of recent formation, all three coats of the artery may be demonstrable; but, as the dilatation increases, the media gradually disappears and the intima and adventitia become more or less thickened from a fibrous hyperplasia. The outlines of the tumor are often quite irregular

from the presence of secondary bulgings at points where the coats are most seriously weakened. Patches showing extensive sclerotic and degenerative changes and calcareous infiltration are generally visible. Fibrinous deposits are usually found in the interior of the sac. As a rule, these are more abundant in saccular than in fusiform aneurysms. In rare cases they completely fill the cavity. The oldest layers of the clot are attached to the intima, are pale, dry, and often laminated; while the most recent layers are nearest to the blood-stream, and are dark in color and soft. Extreme distention of the sac eventually leads to thinning of the coats of the aneurysm and to rupture. Even such an event may not prove immediately fatal, since life may be preserved for a certain period by an adventitious sac which has been formed out of the surrounding tissues.

Aneurysm of the Thoracic Aorta.—Aneurysms of the thoracic aorta are almost invariably associated with arteriosclerosis. Not more than one-seventh of the cases occur in females (17 in 114 cases—Browne). The saccular form is most commonly observed. The size varies from that of a bean to that of a cocoanut. They are usually single, but now and then a half-dozen or more of different sizes are encountered along the course of the vessel.

Aneurysms of the Ascending Portion of the Arch.—This is the portion most frequently involved. The dilatation may arise immediately above the valves, but in a larger number of cases it starts from a point an inch or more from the heart. The innominate artery is rarely involved. In the vast majority of instances the aneurysm springs from the convex side of the aorta and projects to the right; only rarely does it arise from the concave side of the vessel and extend to the left. The structures most liable to be pressed upon are the superior vena cava, pulmonary artery, and left recurrent laryngeal nerve. In about one-third of the cases death results from rupture, the latter occurring most frequently into the pericardium or right pleural cavity.

Aneurysms of the Transverse Arch.—Aneurysms affecting this portion of the aorta usually arise from the right half and from the posterior surface. The innominate artery and ascending arch are but rarely involved. The tumor may extend directly backward, or at other times upward and toward the surface. The structures most apt to be compressed are the trachea, sternum, left bronchus, esophagus, and left recurrent laryngeal nerve. Death from asphyxia is of common occurrence.

Aneurysms of the Descending Portion of the Arch.—Aneurysms of this portion of the aorta most commonly extend to the left and backward, occupying a position in the left interscapular region, close to the spine. The dorsal vertebræ and the ribs are frequently eroded. Other structures liable to be compressed are the esophagus, left bronchus, and trachea. The majority of cases terminate by rupture, which usually takes place into the left pleura, left bronchus, or esophagus.

Aneurysms of the Descending Aorta.—Aneurysms of the descending aorta usually occur a few inches above the diaphragm. As they lie to the left of the lower dorsal vertebræ or immediately in front of them, these bones are often eroded. The larger number of cases terminate by rupture, the latter occurring most frequently into one of the pleural cavities, especially the left, or into the esophagus.

Results.—As aneurysms increase in size, they displace the neighboring

structures or else compress them, and thus set up certain inflammatory and necrotic changes. Some of these effects, however, are purely mechanic. Whether, unaided by other lesions, aneurysms can produce hypertrophy of the heart, is still an unsettled question; but the evidence, both clinical and pathologic, does not favor the affirmative view. In only 72 cases of the 173 tabulated by Browne was there any degree of hypertrophy; and in many of the cases in which the latter was observed, there were valvular lesions present to which the enlargement could be attributed. Aneurysms of the ascending arch occasionally distend the aortic ring to such an extent that aortic valves are rendered incompetent.

On account of the relation which the aorta holds to the trachea and bronchi, the lungs frequently suffer. Death from asphyxia is not uncommon, especially in aneurysms of the transverse arch. Fränkel, who has made a special study of the pulmonary complications of aortic aneurysms, has divided them into four groups: Exudative pneumonia, fibroid pneumonia, gangrene, and tuberculosis. All of these, he states, are dependent more or less upon mechanic causes; that is, the pressure upon the main bronchus. At the point of greatest pressure, necrotic ulceration occurs; and the excretion from this, flowing into the lungs, causes inflammation or coincident infection. Another complication, not alluded to by Fränkel, resulting from pressure upon a bronchus, is bronchiectasis. Compression of the pulmonary artery not infrequently gives rise to pulmonary edema or hydrothorax. Erosion of the sternum, vertebræ, and ribs occurs in many instances. Occasionally an aneurysm of the descending aorta lays open the spinal canal and involves the cord.

The most common termination of thoracic aneurysms is by rupture. The latter was the cause of death in 64 of the 150 cases tabulated by Browne. This accident occurs twice as often in aneurysms of the descending arch and descending aorta as in aneurysms of the ascending and transverse arches; which proves, according to Mir, that the more freely the aneurysm can develop, the more likely it is to rupture. As regards the point of rupture, of the 64 cases analyzed by Browne, the left pleural cavity was the seat in 20, the pericardium in 11, the right pleural sac in 8, left bronchus in 7, the esophagus in 7, the right lung in 3, and the pulmonary artery in 1. In 3 instances the rupture was external, and in 1 into the subpleural connective tissue on the right side. Of 32 cases of ruptured thoracic aneurysm analyzed by Kelynaek, the pericardium was the seat in 13, the left pleura in 7, the esophagus in 3, the trachea in 2, the right pleura, the left lung, the right bronchus, and the superior vena cava in 1 each; in 3 the rupture was external. Of 50 cases studied by Ames and Townsend, in 27 rupture took place through all the coats at once, in 6 through the intima and media primarily and through the external tunic later, and in 8 there was a dissecting aneurysm. Rupture into adjacent blood-vessels is not very rare. Pepper and Griffith have collected 29 cases in which rupture took place into the superior vena cava.

Lamplough cites 16 cases in which aortic aneurysms communicated with the pulmonary artery. Very rarely rupture occurs into the heart, as in a case reported by McPhedran, in which the communication was with the left auricle.

In some instances aneurysms remain latent for an indefinite period.

Williams mentions a patient who had been suffering for thirty years with an aneurysm of the arch of the aorta. Occasionally spontaneous cure results from the complete obliteration of the sac by laminated clot.

Aneurysm of the Abdominal Aorta.—Aneurysms of the abdominal aorta are much less common than those of the thoracic aorta. Of 173 cases of aortic aneurysm collected by Browne from the postmortem records of St. Bartholomew's Hospital, in only 23 was the abdominal aorta involved. The usual seat of the lesion is immediately below the diaphragm, in the region of the celiac axis. It occurred in this position in 20 of the 23 cases noted above. The uniformity in the location of the aneurysm has been attributed to the constriction of the artery at each ventricular systole by the tendinous band which arches over it as it passes between the pillars of the diaphragm, and to the sudden reduction in the lumen of the vessel that is naturally found about an inch and a half below the diaphragm. Erosion of the upper lumbar vertebræ is observed in nearly half of the cases; and in some instances the caries is so extensive that membranes of the spinal cord are exposed.

Aneurysms of the ventral aorta usually terminate by rupture of the sac into the retroperitoneal space or into the general peritoneal cavity. More rarely rupture takes place into one of the pleural sacs, inferior vena cava, intestine, mediastinum, or pelvis of the kidney.

THE VEINS.

Phlebitis.—Acute inflammation of the veins may result from injury or the extension of inflammation from adjacent tissues, or it may be induced by morbid changes in the circulating blood. In the latter cases the disease may be excited directly by the implantation of bacteria from the blood, or indirectly by contact with a thrombus or an embolus. The process is manifested by cellular infiltration of the coats of the veins and a variable amount of necrotic change in the tissue-cells, the intima being more or less affected than the adventitia according as the disease originated as an endophlebitis or a periphlebitis. The lumen of the vessel is very often occluded by a thrombus (*thrombophlebitis*), and this clot may be the primary lesion; but recent bacteriologic studies indicate that in the majority of cases the thrombosis is secondary to the phlebitis. In suppurative thrombophlebitis the thrombus may soften and excite septic embolism. In other cases organization follows, and the lumen of the vein is partially or completely obstructed by cicatricial tissue (*phlebitis obliterans*). A vein-stone or phlebolith is occasionally formed by the calcification of a partially organized thrombus.

Chronic Phlebitis; Phleboscclerosis.—A chronic inflammatory process, characterized by fibrous hyperplasia and analogous to arteriosclerosis, is sometimes observed in the veins. It usually results from prolonged venous stasis or from some chronic intoxication. The most marked examples of the disease have been observed in connection with syphilis.

Varices or Dilated Veins (Phlebectases).—The development of varices is favored by causes which impede the venous circulation and by such morbid changes in the veins themselves as lessen the tonicity of their walls. The vessels most commonly affected are the spermatic, pudendal, hemorrhoidal, and saphena veins. Cirrhosis of the liver, by obstructing the portal

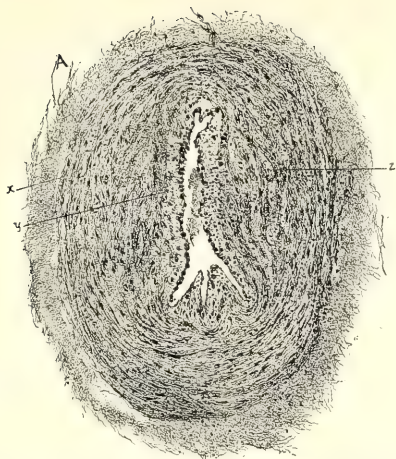


FIG. 175.—Section of vein almost closed by thickening of the muscularis. The thickened muscularis is only partly composed of true muscular tissue, which has been torn apart and thrown into wavy strands by morbid fibroid tissue which has grown in it. *x*, Line of separation of the fibrous coat from the muscularis; *y*, line of separation of the muscularis from the intima. All the tissue between *x* and *y* is muscularis; the thickening is very great. At *y* the separation of muscularis from intima is clearly marked, but at other parts of the circuit there is no distinguishable boundary line. The intima is much thickened, but not so much as the muscularis. The caliber is beaded with endothelial nuclei. $\times 56$ (Meigs).



FIG. 176.—Another section of the vein shown in Fig. 175, showing also great thickening of the walls, but of a different character. The opening is almost filled by irregular projections from the intima. One of these (*o*) is composed of the plicated membrane, which is curiously folded and knotted. There is another somewhat similar knot of smaller size and several irregularly shaped projections of the intima, which fill a large portion of the caliber. The muscularis is irregularly thickened. Parts of it are hard to recognize as involuntary muscle, being more like morbid fibroid tissue. *p* is distinctly muscular tissue; *m* shows the muscularis and intima shading together without a distinguishable line of separation; *n* marks a spot where the separation of the two coats is distinct. $\times 56$ (Meigs).

circulation, frequently occasions varices in the epigastric, mammary, esophageal, and hemorrhoidal veins. Chronic valvular disease, pregnancy, and pelvic tumors are common causes of phlebectases in the vessels of the legs. Local varicosities may be due to occlusion of a large venous trunk by an embolus or to pressure exerted in the vessel from without by a tumor. Atony of the walls of the veins, induced by defective circulation or constitutional disorders, also plays an important part in the development of the disease. At first the veins are simply uniformly dilated, but as the disease advances they become elongated and tortuous. Lateral sacculations are often developed, giving to the vein a knotty appearance. As a rule, the dilatation is accompanied by a thickening of the walls, the result of a fibrous hyperplasia; in some cases, however, the coats of the vessels are perceptibly thinned.

The most important sequences of varicose veins are edema, hemorrhage, thrombosis, and chronic inflammation or ulceration of the surrounding tissues.

THE LYMPHATIC VESSELS.

Lymphangitis.—Acute inflammation of the lymphatic vessels is never a primary disease, but always results from inflammation of surrounding tissues or of parts drained by the affected vessels. In the skin and subcutaneous tissue, acute lymphangitis may be recognized by interrupted red streaks running from the primary focus of infection to the nearest lymph-glands. The minute changes consist in swelling of the intima, proliferation and desquamation of the endothelial cells, and an infiltration of the walls, and often of the surrounding tissues (perilymphangitis), with round cells. Coagulation of the lymph, with the formation of a thrombus, is of frequent occurrence. Slight attacks often end in resolution. In severe septic cases the thrombus softens, the vessel ruptures, and the neighboring parts become infiltrated with pus. Occasionally the process ends in fibroid thickening of the coats of the vessel, with partial or complete obliteration of its lumen (chronic lymphangitis).

Lymphangiectasis.—Dilatation of the lymphatic vessels may be congenital or acquired. The congenital form, which is more of an overgrowth than a dilatation, occurs in the tongue (macroglossia), in the lip (macrocheilia), in the labium, and in other subcutaneous parts. When the formation is more or less circumscribed, it is termed a *lymphangioma*.

Acquired lymphangiectasis results from complete occlusion of important lymphatic channels. Anastomotic communication between the lymphatics is so free in most parts of the body that large vessels, and even the thoracic duct, may be obstructed without serious consequences; only in exceptional cases is the impediment to the flow of lymph sufficient to cause stagnation and to lead to dilatation of the vessels. The obstruction may be due to thrombosis, inflammatory thickening, lodgement of filaria, or to compression of the lymphatic vessels by a tumor. Acquired lymphangiectasis is most commonly observed in the lower extremities and external genitals, where it is accompanied by an enormous hyperplasia of the skin and subcutaneous tissues, and constitutes the disease known as *elephantiasis*.

Tuberculosis.—The extension of tuberculosis from the primary focus of infection is usually effected through the lymphatic channels, and in some instances the vessels themselves are involved in transmitting the disease.

In tuberculous ulceration of the intestines, miliary tubercles are frequently found in the serous coat along the lymphatics which run to the nearest mesenteric glands. Tuberculous lesions of the skin and subcutaneous tissues are sometimes associated with tuberculous lymphangitis. The invasion of the thoracic duct by tubercles may lead to a general infection.

Syphilis and Glanders.—The lymphatic vessels may be involved in the course of syphilis and of glanders.

Tumors.—The two primary growths of the lymphatics are the *lymph-angioma*, to which reference has already been made, and the *endothelioma*; the latter is usually found in the pleura, membranes of the brain, peritoneum, or skin, and may owe its origin to a proliferation of the endothelial cells lining the lymphatic vessels. Cancerous infiltration of the lymphatics may occur in the extension of the disease by metastasis.

Obstruction of the Thoracic Duct.—This results from: (a) Pressure on the duct from without by tumors, enlarged lymph-glands, or aneurysms; (b) the growth of tumors in the walls of the duct; (c) inflammatory stricture; (d) the impaction of adult filaria; (e) thrombosis of the left innominate vein or of the duct itself; (f) the backward pressure of blood in the subclavian vein, occasioned by tricuspid insufficiency.

The results of obstruction to the main lymphatic trunk are variable. In many instances, especially when the obstruction is in the lower part of the duct, the establishment of a collateral circulation averts serious consequences. If for any reason the latter fails to compensate, then extensive lymphangiectasis may follow, or the chyle may escape either by transudation or by actual rupture of the thoracic duct. The free chyle may infiltrate the tissues or may collect in one of the serous sacs, constituting in the peritoneum chylous ascites, and in the pleural sac chylothorax.

THE LYMPHATIC GLANDS.

Retrogressive Changes.—Atrophy and Degeneration.—Atrophy of the lymphatic glands is characterized by a decrease in the number of lymphoid cells. It occurs in old age and in wasting diseases. The glands are small, and, on section, firm from a relative preponderance of fibrous tissue. In some cases fatty infiltration of the reticulum compensates, in a measure, for the loss of substance occasioned by the disappearance of some of the lymphoid elements.

Pigmentation.—Pigments of various kinds are intercepted by the lymph-glands, whither they are brought by the lymphatic vessels. Acute hemorrhagic extravasations, chronic malaria, and Addison's disease are common causes of pigmentation. In many instances the colored particles are extraneous substances introduced into the body from without; thus, the bronchial glands are often deeply discolored by coal-dust and other foreign matter inhaled with the air. The artificial pigments employed in tattooing are sometimes taken up by the carrier-cells and deposited in neighboring glands. The pigment-granules are found chiefly in lymph-sinuses, but ultimately they may appear also in the follicles and even in the trabeculae. Their presence frequently occasions an inflammatory reaction which culminates in a hyperplasia of the connective tissue, partial atrophy of the lymphoid elements, thickening of the capsule, and the formation of adhesions between the gland and adjacent structures.

Calcareous infiltration usually occurs in connection with tuberculous lymphadenitis and other processes which impair or destroy the vitality of the lymphoid tissue. It is occasionally observed, however, in healthy glands when the blood is surcharged with lime salts, as in osteomalacia and extensive caries.

Amyloid degeneration of the lymphatic glands is not uncommon in chronic suppuration. In rare instances the glands alone are affected; but, as a rule, they only share in the process when it is widespread. When the degeneration is sufficiently advanced the glands are enlarged, and, on section, are firm, gray, and translucent. Slight involvement can only be detected by microscopic examination or by the characteristic staining reactions. The walls of the blood-vessels and the trabeculae are the parts affected; the lymphoid cells, though seriously compressed by the amyloid material and even ultimately destroyed by it, rarely if ever share in the transformation.

Hyaline degeneration is sometimes associated with other changes of an inflammatory or degenerative character. It affects chiefly the walls of the blood-vessels and the fibrous tissue of the glands.

Inflammations.—**Acute lymphadenitis** is sometimes excited by the direct extension of an inflammatory process from a contiguous structure. In other cases the primary focus of inflammation is some distance from the affected gland, the irritant having reached the latter through the afferent lymphatic vessels. General infections, such as bubonic plague, diphtheria, scarlatina, and small-pox, are also common causes of lymphadenitis. In these cases the glands in the vicinity of the infection atrium are most seriously affected; but, as the bacteria or their toxins are often widely disseminated, the lymphoid nodes in other parts of the body rarely escape. The inflamed gland is swollen, injected, and soft. On section, the surface is smooth, reddish gray in color, and in severe cases studded with dull yellowish foci representing areas of necrosis.

Microscopically the normal structure is often unrecognizable. The blood-vessels are distended, and hemorrhagic extravasations are observed. The lymph-sinuses are filled with desquamated endothelial cells, red corpuscles, and leukocytes. Round-cell infiltration is apparent throughout the gland. Possibly some of the lymphoid cells proliferate; but many show evidences of a retrograde transformation, which is manifested in the swelling of their protoplasm and in the disintegration of their nuclei. The nuclear fragments are found free and also included within phagocytes, some of which are of enormous size (macrophages). When severe the process ultimately results in complete necrosis; in which case the cells are represented by homogeneous or finely granular areas which no longer possess staining affinities. The formation of fibrin in the coagulated material is sometimes suggested by indistinct fibrillation. When the necrosis is extensive, rupture of the gland may follow; in other cases the dead cells may be slowly absorbed and replaced by scar-tissue, or they may be retained, encapsulated, and subsequently calcified. When pyogenic organisms invade the gland the process may terminate in suppuration. Finally, when the irritation is not severe, but long-continued, the gland may become indurated from a hyperplasia of its connective-tissue elements.

Suppurative lymphadenitis is the result of pyogenic infection. It often occurs in glands whose afferent vessels communicate with infected wounds,

in the inguinal glands in gonorrhea, and in the cervical glands in diphtheria, scarlatina, and glanders. The inflamed gland softens, the septa break down, and the whole structure becomes permeated with pus. In many cases the capsule also gives way, and the purulent contents are discharged into the surrounding tissues, or externally if the gland is superficial. In other cases, before rupture takes place, a fibrinous perilymphadenitis reinforces the capsule, and under these circumstances the pus may become inspissated and perhaps ultimately calcified.

Chronic indurative lymphadenitis may be a sequel of acute lymphadenitis, or it may develop insidiously from the continued presence of foreign matters which have not been sufficiently irritating to excite acute inflammation. The affected gland is usually enlarged, and on section it is firm and



FIG. 177.—Tuberculosis and anthracosis of a lymphatic gland.

dense. The process consists in a hyperplasia of the fibrous tissue, involving the capsule, the trabeculæ, and in some cases the intercellular reticulum. Occasionally the lymphoid cells share in the hyperplasia, but more frequently they suffer retrograde changes from the encroachment of the overgrown connective tissue.

Tuberculous Lymphadenitis.—Tubercle bacilli are conveyed to the lymph-glands through the lymphatics, or probably in rare instances through the blood-vessels. Characteristic lesions are sometimes present about the infection atrium in the skin or mucous membrane; but in many instances the tuberculous process appears to be primary in the glands, the tissues traversed by the bacilli escaping the infection. As a rule, the disease is more or less localized in certain groups of glands; but a generalized form

of tuberculous lymphadenitis is occasionally met with, in which most of the lymph-glands of the body are involved, other structures remaining comparatively healthy. The glands most commonly affected are the cervical, mesenteric, and bronchial. The cervical glands are most frequently infected through the tonsils, carious teeth, nose, or ear; and the mesenteric glands, through the intestinal wall. The bronchial glands are often involved secondarily in tuberculosis of the lungs acquired through the inhalation of infective material; but in some cases, beyond doubt, the pulmonary affection is not the cause, but the result, of a tuberculous lymphadenitis affecting the mediastinal and bronchial glands, which can be traced back to a primary lesion in either the cervical or mesenteric glands. The affected glands are enlarged. In the early stage, section reveals a grayish translucent material distributed uniformly throughout the gland or deposited in the form of discrete nodules. Later, caseation follows, and this material becomes yellowish white in color, opaque, and friable.

The process often terminates, especially in children, in softening of the caseous patches and rupture of the gland. At other times a reactive inflammation brings about an overgrowth of the connective-tissue elements of the gland and thickening of the capsule, and under these circumstances the necrotic tissue may in time become impregnated with lime salts.

Microscopically the chief features are the presence of epithelioid cells and giant cells surrounded by a round-cell infiltration. Bacilli are only visible in the early stages of the disease, and then they are found in and between the cells. In some cases, especially of cervical adenitis, the cellular proliferation is chiefly of the epithelioid type, round cells being comparatively few in number; under these circumstances, caseation is slow in appearing, and, as a result, the glands remain enlarged and indurated for an indefinite period. After necrotic changes have become well established, examination reveals granular or structureless areas wholly void of cellular elements and surrounded by zones of overgrown fibrous tissue in which pigment-granules are often present.

Syphilitic Lymphadenitis.—The lymph-glands in the neighborhood of the primary lesion are always swollen and indurated. In the secondary period a more or less generalized lymphadenitis is present; but there is nothing to distinguish it pathologically from other chronic forms of the disease. In the tertiary period the lymph-glands are occasionally the seat of a true gummatous formation. Amyloid degeneration of the lymph-glands is sometimes observed in connection with the inflammatory changes incident to syphilis; it affects chiefly the walls of the blood-vessels and the interstitial reticulum.

Tumors.—**Lymphadenoma; Lymphosarcoma.**—These terms are used to designate certain enlargements of the lymphatic glands dependent upon a hyperplasia of their lymphoid elements. The true character of these growths has not been determined. Although no micro-organism has been definitely associated with the affection, its resemblance to tuberculosis has suggested an infective origin. The glands most frequently involved are the cervical, axillary, inguinal, mediastinal, and retroperitoneal. In many instances growths of lymphoid tissue are also found in the various organs, especially in the spleen, liver, and kidneys. The affected glands vary in size from that of an almond to that of an egg; they may be either hard or soft. For a long time they remain isolated, freely movable, and unattached to the over-

lying tissue; but ultimately they become united to one another and to adjacent structures by inflammatory adhesions. Caseation and softening are rare, but not infrequently the lymphoid growth breaks through the capsule and infiltrates surrounding parts. On section, the glands are smooth, somewhat opaque, and of a grayish-white or reddish-gray color. When they are soft the cut surface yields, on scraping, a milky fluid not unlike that obtained from cancerous growths. Fibrous glands are firm and dry.

Microscopically the characteristic feature is a great increase in the number of lymphoid cells. The latter lie closely packed in the meshes of the reticulum and do not differ materially in appearance from the normal cells. In the early stages of the disease the structural relations are not altered to any great extent, and medulla, follicles, and septa are readily differentiated; later, in many cases, all histologic divisions are obliterated and the specimen

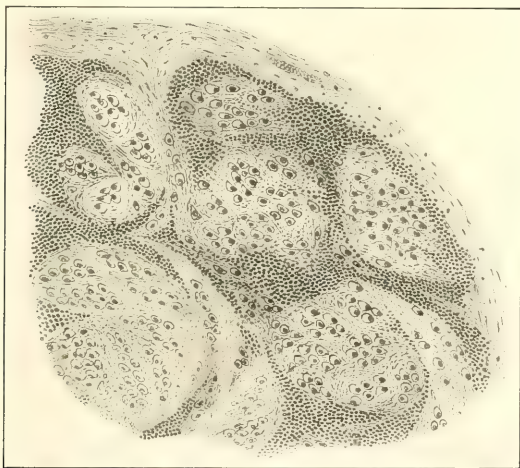


FIG. 178.—Carcinomatous infiltration of a lymph-gland.

presents a uniform aggregation of small round cells embedded in a fibrillar network. In some cases, however, the connective-tissue elements, instead of being reduced by encroachment of the lymphoid cells, undergo proliferation, thus rendering the gland firm and elastic.

Apart from the local disturbance excited by the glandular enlargements, changes in the composition of the blood sooner or later develop. The red cells fall off considerably in number, while the white cells remain approximately normal or are enormously increased. According as the oligocythemia is or is not accompanied by a leukocytosis, two forms of the disease have been recognized clinically, namely, leukemia and pseudoleukemia or Hodgkin's disease.

Le Count¹ has described a benign tumor resembling the lymph-glands in structure—a true lymphoma.

¹ *Jour. of Exper. Med.*, iv., 559, 1899.

Sarcoma.—This is the only primary growth of the lymphatic glands. Excluding the so-called lymphosarcoma, to which attention has already been directed, the principal forms are the round-cell, spindle-cell, and alveolar sarcoma. While several glands in the same group are often affected, there is very little tending, as in the lymphosarcoma or lymphadenoma, to involvement of neighboring glands; indeed, before the latter occurs, the tumor often breaks through the capsule and invades surrounding tissues, and even gives rise to secondary growths in distant organs. Sarcomas originate in the walls of the blood-vessels or in the connective-tissue reticulum. Secondary or metastatic growths are also encountered in the lymph-glands.

Carcinoma.—The lymphatic glands are the favorite seats of secondary cancer. Cells from the parent tumor are carried through the lymphatics to the nearest gland, where they multiply and are formed into nests by a fibrous stroma derived from the lymphadenoid tissue.

THE SPLEEN.

Congenital Anomalies and Displacements.—Complete absence of the spleen is rare. Hodenpyl, in reviewing the nine cases collected by him of apparent absence of the spleen, shows that only one can be accepted without question as an instance of this condition. In these cases the organ is usually represented by several small, scattered masses of splenic tissue (splenunculi), which, on account of their size and location, are in danger of being overlooked. More often, splenunculi are present in addition to the normal gland; they vary in number from three or four to a dozen or more, and are embedded in the peritoneal folds, omentum, the wall of the intestine, or, as in a case described by Biggs, in the tail of the pancreas. Abnormalities in shape, including marked lobulation, are sometimes observed. Rolleston describes a remarkable malformation in which the spleen gave off a long process extending down into the scrotum. In some instances the spleen occupies the right side of the abdomen, and the liver the left. According to Gruber, transposition of these organs occurred in 70 of 78 cases of dextrocardia.

Movable Spleen.—Movable spleen is seen most frequently in association with gastropotosis and enteroptosis, but it may occur as an independent affection. Relaxation of the ligaments from enlargement of the organ or from congenital weakness is the chief cause of the condition. A wandering spleen is usually found a little below its normal position, but in exceptional cases it may be as low as the pelvis. Sometimes the development of inflammatory adhesions serves to fix the spleen in its abnormal position. Twisting of the pedicle may cause, as in a case cited by Osler, hemorrhagic infarction and extensive necrosis.

Circulatory Disturbances.—Anemia.—This occurs as a part of general anemia, and is manifested by unusual pallor of the pulp.

Hyperemia.—*Active hyperemia* as a pathologic condition is most frequently seen in the specific fevers and septicemia. It is intimately associated with acute inflammation of the organ. *Passive hyperemia* occurs in the course of visceral diseases which impede the venous circulation, such as chronic valvular disease, emphysema, and cirrhosis of the liver. In the last affection, however, the enlargement of the spleen may be due in part, as Weber suggests, to a toxemia. The spleen is enlarged, firm, and of a

dark-red color. Section reveals distention of the veins, and often extensive pigmentation from the disintegration of red blood-cells. When long-continued, the organ becomes very hard and tough from hyperplasia of the fibrous tissue and secondary condensation and atrophy of the pulp (cyanotic induration).

Infarction of the Spleen.—The most common cause of splenic infarction is the plugging of a branch of the splenic artery by an embolus derived from the left heart or aorta. Thrombosis of the splenic artery, a condition occasionally met with in acute infective diseases, is a much less frequent cause of infarction. Thrombosis of the splenic vein, excited by inflammatory processes in contiguous organs or by extension of a thrombus from the portal vein, is a rare cause. Osler has recorded a case of splenic infarction induced by twisting of the pedicle of a movable spleen. The area of coagulative necrosis is generally wedge-shaped, with the base directed toward the surface of the organ; it projects somewhat beyond the surface of the surrounding tissue, and its consistence is more or less increased. The color of the infarct depends upon the variety: in the anemic form, which is the more common, it is dull white; in the hemorrhagic form, it is dark red from the extravasation of blood. The lesions may be single or multiple, and vary in size from that of a millet-seed to a bulk equal to more than one-half of the entire organ. Infarcts caused by noninfective emboli slowly disintegrate and are replaced by connective tissue, the site of the lesion being eventually marked by a whitish scar-like patch. Infarcts excited by infective emboli are speedily converted into abscesses. Thrombosis of the splenic vein or of its large branches results in total necrosis and hemorrhagic infiltration of the spleen.¹

Hemorrhage.—Traumatism and infarction are the most common causes of hemorrhage into the substance of the spleen. Small extravasations occur also in acute infective splenitis.

Retrogressive Changes.—Atrophy.—Simple atrophy occurs in old age and in wasting diseases. The organ is small, the capsule is wrinkled and opaque. On section, the substance is pale and the stroma conspicuous. Microscopic examination reveals atrophy of the Malpighian bodies and of the pulp, and an actual or relative increase in the fibrous trabeculæ.

Pigmentation.—The most marked hematogenous pigmentation of the spleen occurs in malarial cachexia, the granules being deposited in the trabeculæ, especially around the blood-vessels, and likewise in the lymphoid cells. Pigmentation is also one of the sequels of chronic venous congestion. In pernicious anemia and other severe cachexias associated with exaggerated hemolysis the condition is often well marked. Foreign substances, such as coal-dust, may reach the spleen through the blood and be deposited in the wall of the arteries.

Amyloid Degeneration.—Two forms are recognized: (1) The *sago* spleen, in which the capillaries of the Malpighian bodies are the parts chiefly affected; and (2) the *diffuse* form, in which the disease is more or less limited to the capillaries and veins of the pulp. The sago spleen is somewhat enlarged, its consistence is increased, and on section it is studded over with grayish translucent bodies varying in size from that of a pin's head to that of a millet-seed and closely resembling grains of sago. In the diffuse form of the disease, which is the less common, the organ is often

¹ Christomonas, *Ziegler's Beiträge*, xxiv., 519, 1899.

considerably enlarged ; its structure is dense, and on section it presents a homogeneous, waxy, semitranslucent appearance. In this variety the Malpighian capsules usually escape, the disease beginning in the small vessels of the pulp, spreading to the trabeculae, and finally, in rare instances, involving the pulp itself.

Hyaline degeneration is sometimes observed in the walls of the vessels and in the reticulum of the pulp.

Inflammations.—**Acute Splenitis.**—Acute nonsuppurative inflammation of the spleen frequently occurs in the course of infective diseases. The organ is enlarged, sometimes to three or four times its normal size, and the capsule is distended. On section, the tissue is at first firm and of a dark-red color ; but as the process advances the pulp becomes soft and even diffuent, the color pales, and the Malpighian bodies appear abnormally prominent or are covered by the swollen pulp. Extensive hemorrhagic extravasations are not uncommon. Microscopic examination reveals an

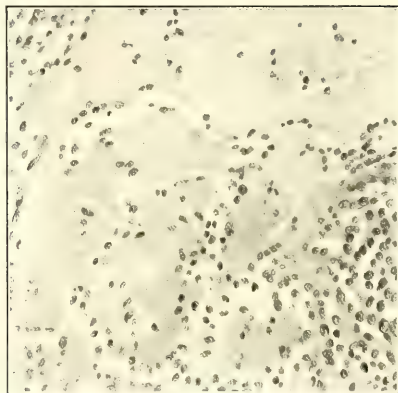


FIG. 179.—Amyloid degeneration of the spleen.

overdistention of the vessels, marked proliferation of the cells, both of the pulp and of the Malpighian bodies, and emigration of round cells. Degenerative changes appear early ; these are shown in the fragmentation of the nuclei, the disintegration of the cells, the loss of affinity for nuclear stains, and in the presence of cellular detritus and pigment-granules, which are found free and enclosed within phagocytic cells. Acute splenitis usually terminates in resolution ; but rupture of the organ, suppuration, and fibrous hyperplasia are possible sequels.

Purulent Splenitis.—Abscess of the spleen most frequently occurs in the course of some septic process, such as ulcerative endocarditis or general pyemia, the vehicle of infection being an embolus loaded with pyogenic micro-organisms. It is rarely a sequel of the acute splenitis which accompanies typhoid and other specific fevers. Traumatism is an occasional cause. Inflammatory affections of adjacent organs may extend to the spleen and excite suppuration ; in this way, gastric ulcer has given rise to abscess.

Embolic abscesses are usually multiple, and are situated near the periphery of the organ. Their formation is almost invariably preceded by infarction, the dead tissue being subsequently converted into a grumous reddish fluid. Occasionally splenic abscesses become encapsulated and subsequently transformed into caseous or calcareous nodules; but a much more frequent termination is perforation of the abdominal walls, or discharge of the pus into the peritoneum, stomach, colon, pleura, or lung.

Chronic Interstitial Splenitis.—Diffuse hyperplasia of the connective tissue may result from repeated attacks of acute splenitis, as in malaria, or from long-continued venous stasis, as in cirrhosis of the liver. General fibrosis is also observed in late syphilis and in rickets. Circumscribed areas of fibroid induration often mark the site of old infarcts. The spleen is enlarged and its consistence is increased. The capsule is usually thickened, and adhesions occasionally unite the organ to the adjacent structures. On section, the substance is firm, smooth, and often dark in color from the presence of free pigment. Microscopic examination reveals a great increase in the trabecular tissue and pigmentary infiltration of both pulp and connective-tissue cells.

Tuberculosis.—Acute miliary infection often occurs in general tuberculosis. The organ is studded, especially in the neighborhood of the capsule, with small gray tubercles, which may bear a close resemblance to the Malpighian bodies. Chronic tuberculosis is manifested by the presence of grayish-yellow caseous masses varying in size from that of a pea to that of a walnut. They may break down in the center and become semidiffuent; or, as in other organs, they may calcify. In the chronic form there is often extensive fibrous overgrowth.

Syphilis.—This disease may be manifested by gummatous growths or as a diffuse fibrous hyperplasia. Gummas are rare; Still was able to collect but 26 recorded cases; 20 of these were associated with acquired syphilis, and 6 with the hereditary form of the disease. The growths may be single or multiple, and vary in size from that of a pea to that of an egg. When the gumma is near the surface of the spleen the capsule is thickened, and adhesions often unite the organ to adjacent structures. Diffuse fibrous hyperplasia is of common occurrence in hereditary syphilis. The organ is large and tough, and its capsule is usually thickened. Amyloid degeneration is often seen in the acquired form, but it is rare in congenital syphilis.

Tumors; Cysts.—**Lymphadenoma** or **lymphosarcoma** is observed in leukemia and pseudoleukemia. The spleen is enlarged and usually firm; adhesions often unite it to the diaphragm and neighboring organs. The capsule may be thickened. The Malpighian bodies are enlarged into grayish-white opaque nodules, quite irregular in shape, and varying in size from that of a pea to that of a walnut. Infarcts are often present. Microscopic examination reveals great numbers of lymphoid cells, which are contained in the meshes of a fibrous reticulum. The trabeculae also are increased in size. Large nodules compress the surrounding pulp and bring about degeneration and pigmentation of the cells.

Carcinoma and **sarcoma** of the spleen are rare. The former is probably always secondary; the latter has been observed as a primary growth, but in the large majority of cases it is secondary.

Fibromas and **lymphangiomas** have been described.

A unique instance of **cavernous angioma** has been recorded by Langhans.

Cysts.—The small serous cysts occasionally found near the surface of the spleen are possibly due to dilatation of the lymphatic vessels or to the inclusion of small portions of peritoneal endothelium.

Extravasation-cysts are the result of traumatism.

Animal Parasites.—*Echinococcus*, *cysticercus*, and *Pentastomum denticulatum* occur.

Of 1771 cases of hydatid disease collected by Sommer, the spleen was affected in 42.

THE NERVOUS SYSTEM.

GENERAL INTRODUCTORY REMARKS ON THE PATHOLOGY OF THE NERVE-CELL.

IN discussing the reaction of the nervous system to excitants of disease, much will be said about the neurone and the changes it undergoes in its struggle to maintain a physiologic state. As these changes are somewhat different from those in other tissue the seat of similar disease, because of the origin and constitution of nerve-parenchyma, it is advisable, in order that many statements in the text may be readily comprehensible, to present a brief description of the neurone and to make mention of the technic that has given us our present information. The cells of the nervous system have been diligently studied in many diseases; but it was not until methods of staining with anilin dyes, methylene-blue, thionin, toluidin-blue, and modifications of the sublimate method of Golgi, that any considerable progress was made. The older methods failed to reveal the finer cytologic changes at the bottom of nervous diseases; unfortunately the new methods have not yet entirely encompassed the problem, but they have helped us to take a great step forward.

The term *neurone*, or unit of the nervous system, is now universally used to denote the whole nerve-cell and all its processes. Each neurone is an independent entity having no connection with other neurones save by contiguity. It is composed of a cell-body made up (enumerated from within) of the nucleolus, nucleus, chromatic substance (Nissl bodies), achromatic substance (constituting the greater part of the cell-body), the pigment, the protoplasmic (dendritic) processes and their gemmules, and the axis-cylinder process, its collaterals and terminal arborizations. Each of these components of the cell offers different degrees of resistance to excitants of disease. The protoplasmic processes intermingle and intertwine with each other, and have their distribution in the immediate vicinity of the cell-body from which they arise. They are nutritive in function and conduct toward the cell—*i. e.*, centripetally. Their functional activity is connected with bead-like substances upon them, known as gemmules or spines, thorns, lateral buds, and pyriform processes, which increase the surface of connection of the protoplasmic arborizations. The neuraxones (axis-cylinder processes), one for each cell-body, give off *collaterals* at various levels in their course, and have their eventual distribution in arborizations, usually around other cells, generally at some distance from the cell-body from which they take their origin. They are functionally centrifugal.

Formerly it was thought that the protoplasmic processes interlaced and anastomosed to form the network of Gerlach, and that the branches of adjacent axis-cylinder processes anastomosed to form the diffuse network of Golgi, and that these were the pathways of intercommunication. The

neurone doctrine is not universally accepted. Golgi has opposed it; and Held has done much work which seems to discredit it in part. Recently Apathy has set forth the results of his investigations, which go to show that the neurone doctrine cannot be accepted unconditionally, at least without considerable modification.

These views of Apathy can be referred to here only in the briefest manner. He divides nerve-cells into two kinds, nerve-cells proper and ganglion-cells. From the nerve-cells proceed neurofibrils; these arise from the processes of the nerve-cells and pass through a number of ganglion-cells, ultimately leaving the last ganglion-cell to enter a muscle or a sensory cell. The neurofibril is therefore a continuous, uninterrupted structure throughout its entire course. In passing through a ganglion-cell it enters by the axis-cylinder process, coils round and round in the interior of the cell, and then leaves by the axone process by which it entered the cell. Inside the ganglion-cell a reticulum of fine fibrils, derived from the neurofibrils in transit, can be easily perceived by his method of investigation. The ganglion-cell therefore supplies the force which is to be conducted along the neurofibrils. Apathy's work has been done exclusively on invertebrates, principally the leech, in which the cells are unipolar. In other animals, however, in which the cells possess dendrites entirely separate from the axones, the neurofibrils enter the cells by way of the dendrites, ramify and anastomose freely inside the cell-body, and then, reuniting, take their exit by way of the axone. Each neurofibril is made up of a number of elementary fibrils; and as, during its course, these are being constantly given off, the neurofibril may ultimately become reduced to a single fibril. Thus, one nerve-cell may, by means of one or more elementary fibrils, be put into connection with several ganglion-cells. But, while one ganglion-cell may be put into connection with several nerve-cells, an end-organ cell is never connected directly with more than one nerve-cell.

Structure of the Nerve-cell.—The cell-body consists principally of two kinds of substance: one which stains darkly with methylene-blue, the chromatic substance; and one the preponderant portion of which does not stain, the achromatic substance. The chromatic substance (Nissl bodies or chromophilic substance or tigroid) presents itself in many forms: irregular particles, smooth or dentate fibers, spindles, wedges, stellate, dumbbell-shaped masses, striate, concentric, and reticular in arrangement. It lies within the interstices of the intracellular network. Different types of cells possess it to a different degree. The small ganglion-cells contain it less than the large cells.

The function of the chromatic substance has not yet been definitely determined. The achromatic substance, which constitutes the greater part of the cell-body, is made up of fine fibrils passing diametrically through the cell, with numerous anastomoses, which give it a finely reticulated appearance. This reticular structure in all probability represents the true cellular protoplasm. (It is maintained by some (Held and others) that the fibrils are in reality rows of fine granules.) It is not improbable that the reticulated fibers are the continuation of the axones on their way into the protoplasmic processes. This view makes it the all-important part of the cell. In addition to this, the cell-body contains a variable amount of pigment, of which two varieties have been distinguished: one, a pale yellow, found in the cerebral cortex, basal ganglia, spinal cord, and sympathetic ganglia; the other, dark brown, occurring in the substantia nigra. The pigment is found in clusters, chiefly at the point of emergence of the processes. The nucleus of the cell is of different size in cells from different parts of the nervous system. It is usually seen in the center of the cell, but an excentric position cannot be considered a certain manifestation of disease. With methylene-blue it is seen to consist of a distinct nuclear membrane and a large central nucleolus which stains very deeply.

Under the influence of injurious agencies the various constituents of the cell undergo changes to which different names are given. The full significance of these changes has not yet been fully determined; but, as they are frequently referred to in this section, it is deemed necessary to make some mention of them here by way of introduction.

The constituent of the nerve-cell that is most susceptible to harmful influences are the Nissl bodies. Disintegration of them is known as *chromatolysis*. This change may go on in various parts of the cell, and it is often spoken of as peripheral, perinuclear, and disseminated. It may be partial or complete, acute or chronic. The mechanism of chromatolysis is still obscure; but it is generally believed that the process represents the reaction of the cell to a disturbing force, and, although it is a condition that is reparable, during its existence the parts affected are deprived of functional activity. Achromatolysis or plasmolysis is a step further than chromatolysis, and is the term applied to the simplest disorganizing changes in the achromatic part of the cell. The next stage in disorganization of the achromatic substance is coagulation, hyaline transformation, and intense colorability of the achromatic substance. It is highly probable that, when any of these changes occurs in the achromatic substance, the cytoplasm is beyond repair.

Other changes are vacuolation, fatty degeneration, pigmentation, and displacement and homogeneous transformation of the nucleus. Vacuolation consists in the formation within the cell substance, either the nucleus or the protoplasm, of one or more nonstainable globules of a fluid character. Their causation and significance have not yet been satisfactorily determined. Fatty degeneration is a step beyond vacuolation. The significance of pigmentation or pigmentary degeneration of nerve-cells is not known. In some cells pigment forms a physiologic constituent, as, for instance, in the cells of the substantia nigra and ferruginea. By some (Bevan, Lewis, and others) it is considered indicative of functional hyperactivity, while the majority consider it the product of metabolism in the cell and identical with one or more of the slowly progressive forms of chromatolysis.

When the achromatic portion of the cell becomes disorganized so as to impair the reticulum that holds the nucleus in place, the latter becomes dislocated. It may be completely extruded. But many investigators attach too much importance to displacement of the nucleus. Certainly it often accompanies pathologic conditions, but not invariably so. When the substance of the nucleus undergoes homogeneous transformation, the process may be considered as advanced. Degeneration of the nucleolus results from lesions that the nucleus itself withstands, and disorganizing changes of the nucleus almost always appear first in the nucleolus as vacuolation. The nucleolus may be represented finally by a mere clump of pigment by the time the nucleus begins to show evidence of disease.

Morbid alterations of the processes of nerve-cells, dendrites, and axonones are revealed by the Golgi, Nissl, and Marchi stains. The alterations revealed by the Golgi stain are, in the protoplasmic processes, varicosities or varicose atrophy and the disappearance of the gemmules of the terminal filaments. Although there can be no question that these conditions are significant of pathologic states, it is also certain that they may be produced artificially, and indeed are often of such origin. In the axones the Golgi method is capable of showing globular, fusiform, or irregular swelling, called

varicose hypertrophy, which, in a moderate degree at least, is not necessarily a pathologic condition.

Much experience and great caution are required to put adequate and proper interpretation upon the changes revealed by the modern methods of investigating nervous cytology. There are yet to be determined (1) the constitution of the normal cell and its reaction to stains; (2) the constitution of the fatigued cell or the cell in different stages of functional activity; and (3) postmortem changes, especially those more or less immediate. It is beyond question that some of the changes that have been described by writers as incident to disease have been the result of postmortem disintegration, and some of immediate antemortem conditions, such as hyperpyrexia. It has been convincingly demonstrated that such disintegration is manifested by swelling of the cell-body, progressive loss of staining capacity of the Nissl granules, vacuolation of the protoplasm, indistinctness and irregularity of the nucleus, fragility and fracture of the protoplasmic processes, and finally loss of the staining capacity of the cell, perhaps its complete disappearance. Thus it will be seen that the conditions may not be unlike those described in pathologic states. They may be differentiable, however. The post-mortem changes are apt to be more general and uniform, there is no diffuse granulation of the cytoplasm, no round-cell infiltration, and no hyperplasia of the neuroglia.

MALFORMATIONS OF THE SPINAL CORD.

Malformations of the spinal cord are much commoner than those of other portions of the central nervous system; they may be congenital or acquired. The congenital forms are of interest to teratologists, but not so much so to the physician, except the form known as true heterotopia, which has sometimes been made responsible for symptoms. The central nervous system, in being removed from the body and in preparation for the microscope, not infrequently suffers artificial changes. These changes so often simulate morbid conditions produced by disease, that in a number of instances they have been regarded as the anatomic basis of the symptoms. These facts make a brief consideration of the subject necessary.

Van Gieson has recently investigated this subject with great diligence, and the writer will quote from his essay on Artefacts of the Nervous System.

The malformations of the spinal cord may be classified as follows:

I. Congenital Deformities Associated with Monstrosities and Incompatible with Extra-uterine Life.—These may be divided into:

1. **Amyelia**, or absence of the spinal cord. This is almost invariably associated with absence of the brain.

2. **Atelomyelia**, or partial development of the spinal cord. This is often seen in anencephalic or acephalic monsters, where, corresponding to the incompletely developed brain, there may be various degrees of defective development in the length of the cord.

3. **Diastematomyelia**, a condition in which a portion or the whole of the cord is split into two lateral halves, each half of the cord being enveloped in its own membranes and giving rise to its own nerve-roots. The halves may fuse together at some point to form a single cord.

4. **Diplomyelia**, or a formation of two spinal cords—a duplication of the spinal cord. This happens in the various kinds of double monsters.

II. Minor Congenital Malformations Not Inconsistent with the Maintenance of Life.—These may or may not be recognizable during life, and may be subdivided as follows:

1. **Hydrorrhachis interna**, or **hydromyelia**, which is considered under Cavities of the Spinal Cord.

2. **Hydrorrhachis externa** consists in an abnormal congenital accumulation of fluids between the meninges of the cord, causing more or less diminution in the volume of the latter.

3. **Heterotopia**, or misplacement of the substances of the cord.

(a) There may be misplaced portions of the gray matter. Minute bits of gray matter or of the gelatinous substance of Rolando may develop in the white columns of the cord. These may be isolated or partially connected with the gray horns by slender gray filaments.



FIG. 180.—False heterotopia, showing dislocation of the column of Clarke (author's collection).

(b) Portions of the white matter may be arranged in an unusual manner. This malposition of bundles of white matter or the passage of bundles of nerve-fibers through unusual channels to reach their prescribed destinations is almost exclusively observed in the isthmus.

4. **Anomalies** of the spinal nerve-roots. These are not extensive and are usually of the anterior roots.

5. **Asymmetries** of the spinal cord.

III. Malformations of the Spinal Cord Acquired During Extra-uterine Life or Secondary to Defective Development of Other Parts of the Body.—The acquired distortions of the substance of the cord may be roughly divided into:

1. **Distortions** which follow certain cord-lesions. The substances of the cord, it has been mentioned, especially the gray matter, may be distorted or misplaced in a number of the spinal diseases.

2. **Asymmetric conditions** of the cord due to arrested development of the cord after birth or secondary atrophy of portions of the cord corresponding to defective development or absence of some part of the body elsewhere. In cases of intra-uterine amputations the corresponding portion of the

cord is asymmetric if the individual has lived a number of years. The gray and white matter, particularly the former, is shrunk in the corresponding half of the cord. A slight asymmetry of the cord is found a number of years after ordinary surgical amputations. Cases of congenital club-foot have been described with slight asymmetry in the adult cord, due to a trifling shrinkage of the anterior horn on the corresponding side.

3. **Variations in the volume** of the cord as a whole, as to the length, thickness, position in the vertebral column, and configuration of the external furrows and fissures, occur, apparently dependent upon the variations in the physical development of different individuals.

False Heterotopia.—The great merit of van Gieson's work has been to show that the vast majority of cases described in the literature as cases of heterotopia are in reality artefacts, the result of manipulation during removal of the cord, true heterotopia being extremely rare.

In **true heterotopia** the gray horns are not misshapen, nor are there any deficiencies. They have the typical contour and symmetry; there is simply a redundant bit of gray matter which was left behind during the development of the spinal gray matter. In false heterotopia the horns are misshapen and pieces of dislocated gray matter can be traced to corresponding deficient areas of the cornua. The misplaced matter is surrounded by mechanically deflected tracts of white matter. These conditions are shown by the accompanying illustration (Fig. 180), in which the false heterotopia was slight.

DISEASES OF THE SPINAL CORD.

Introduction.—The spinal cord is a portion of the nervous system very susceptible to disease. The fact that it is made up of extraspinal constituents (the posterior columns) and cerebral constituents (the motor tracts) as well as a special spinal substance (the ganglion-cells) exposes it to the manifestations of many diseases, the immediate seat and causes of which may be in remote parts of the body. For example, cerebral apoplexy produces secondary degeneration in the cord; multiple neuritis of toxic origin is often accompanied by recognizable changes in the cord; and the lesion of tabes dorsalis, a disease always spoken of as of the spinal cord, is, anatomically speaking, in reality a disease of fibers of extraspinal origin in their intraspinal course. Then again, the arterial blood-supply of the cord and the return venous and lymph circulation have peculiarities that predispose, or at least facilitate, perversions of its function. These peculiarities will be discussed when speaking of the different diseases of the cord.

The spinal cord is liable to compression from diseases that interfere with the integrity of the bony canal in which it is encased, and naturally it is quick to suffer destruction when injuries from without, such as stab and gunshot wounds or penetrating fracture, implicate it. It is the organ principally affected in the condition called caisson disease. In these cases the lesion is one of true hemorrhagic myelomalacia, the destruction of tissue being secondary to rupture of blood-vessels caused by perversion in the relationship existing between blood-pressure and atmospheric pressure in delicate arteries having but slight support.

The blood-vessels of the spinal cord are seemingly more susceptible to the injurious action of certain poisons taken into the system from without

or generated within the body than other vessels are, so that evidences of arterial degeneration from such conditions as gout, rheumatism, and syphilis are not rare. It is, however, the remarkable susceptibility that some constituents of the spinal cord have to certain poisons generated outside of the body that is most difficult of interpretation. Clinical experience has taught us that syphilitic infection precedes the development of *tabes dorsalis* in about nine-tenths of all cases, and pathologic investigation has shown that the morbid anatomy of this disease has nothing in it remotely suggestive of syphilis. On the other hand, the investigations of Tuzcek and others have shown that one of the sequences of continued slow absorption of ergot is a degeneration of the posterior columns. The researches of Stieglitz and others tend to show that the ganglion-cells of the anterior horns have a somewhat similar susceptibility to the metallic poisons, particularly lead. All these facts must be borne in mind in endeavoring to interpret morbid changes in the spinal cord.

Myelitis.—The term myelitis in its restricted sense signifies inflammation of the spinal cord. The term has been used loosely to include all softenings of the cord, whether due to pressure or to inflammation. Myelitis, in the broad sense, is a common disease, but rare if the term is restricted to inflammatory exudations.

Myelitis may be classified according to the seat of the lesion; if predominantly of the gray matter, into *poliomyelitis*; if of the white, into *leukomyelitis*; according to the extent of the lesion, into *diffuse myelitis*, in which the lesions involve nearly all the tissues of the cord and are attended with profound tissue destruction; into *transverse myelitis* when the greater number of constituents of the cord to be seen on cross-section are involved, the lesion limiting itself in the longitudinal direction to one segment or metamere of the cord. Transverse myelitis is sometimes subdivided, also, according to the distribution of the lesion into *central* or *ependymal myelitis*; *annular myelitis*, the lesion being limited to a peripheral zone; and *hemilateral myelitis*; and according to the region of the cord in which it is found, into *cervical*, *dorsal*, *lumbar*, and *bulbar transverse myelitis*. Clinically and pathologically, it is spoken of as *apoplectic*, *acute* or *chronic*, according to the intensity of the disease process; while etiologically it may be referred to as *toxic*, *infectious*, *traumatic*, and *compression myelitis*. The toxic varieties have been divided, according to Plessner, into four groups: 1, *Toxic poliomyelitis*; 2, *disseminated toxic myelitis*; 3, *pellagrous myelitis*; and 4, *ergotinic myelitis*, so-called *ergot tabes*. The micro-organisms that have been found in the myelitic focus are the *streptococcus*, the *Staphylococcus aureus* and *albus*, the *pneumococcus*, a special *diplococcus* described by Buzzard and Russell, and the *tubercle bacillus*.

It will materially facilitate the conception of myelitis to discuss briefly, first, infiltration and edematous states of the cord arising from inflammatory and noninflammatory conditions.

Compression of the spinal cord results from tumors, particularly those of the meninges and vertebræ; tuberculosis of the vertebral column; some forms of meningitis, especially hypertrophic cervical pachymeningitis; from aneurysms and from tortuous, dilated, atheromatous arteries, especially in the region of the *oblongata*. All of these may cause tumefaction of the nerve substance, resulting in partial or complete destruction, the consequence of stasis and edema, inflammatory or noninflammatory, which they cause.

The changes that take place in the cord as the result of mechanic and inflammatory edema have been carefully studied. If a nerve-fiber is placed in a serous fluid or in a solution of common salt, the following changes will be seen to occur: Swelling of the fiber, separation of the myelin into drops, segmentation of the axone, and eventually disintegration of the entire substance, neurokeratin alone remaining. Rumpf has shown that a segment of a frog's spinal cord that has been separated from its roots within the living body eventually becomes entirely absorbed. These experiments have been made the basis of a theory to explain the changes in the spinal cord when subjected to slight but continuous pressure; in other words, to explain the pathogenesis of compression myelitis. In such condition there result mechanic stasis of the lymph circulation and a consecutive softening of the cord.

In some cases the edema is so marked that the tissue is destroyed and genuine myelomalacia results, with cellular infiltration, constituting a form of myelitis which cannot be distinguished without consideration of the cause and the genesis of the condition from true inflammatory myelitis. Usually, however, the succession of changes is comparatively slow, destruction of tissue being gradual and not attended by softening unless the compression is due to some profound injury, such as fracture or dislocation of the spinal column.

The myelitic or degenerative changes that occur from interference with the lymph circulation, the so-called lymphogenous form of myelitis, have been carefully studied as they occur in pernicious anemia, leukemia, persistent jaundice, chronic nephritis, carcinoma, amyloid degeneration—in short, all wasting diseases. The distribution of the lesion in these cases is not characteristic. It may occur in any part of the cord, the white or gray substance, as well as in the nerve-roots. The lesions have a striking predilection for the posterior and lateral columns. The neuroglia loses its fibrillated structure, its fibers become fragile and crumpled, the fibrillae being irregularly swollen and granular. The glia-cells are swollen, and numerous corpora amylacea form. The myelin of the nerve-sheaths runs together, and the sheaths become varicose. The neuraxones become swollen and often present a spiral, corkscrew-like appearance. As the process goes on the medullary substance separates into drops which oftentimes press the axone to one side. The condition is brought about by a severe degree of edema.

Acute Myelitis.—Acute myelitis may be localized or diffuse. It may follow infections, such as typhoid fever, dysentery, influenza, tonsillitis, and pneumonia. It may result from hydrophobia, gonorrhea, and purulent affections of the urogenital organs. It may be caused by embolism of the cord, which has its origin in endocarditis or in purulent or tuberculous processes in the lungs. Sometimes it follows refrigeration, alcoholic and sexual excesses, and it may be secondary to acute meningitis and to ascending neuritis. At times, no cause is ascertainable. It is more than probable that one form of myelitis, acute poliomyelitis, is dependent upon a specific organism, and that certain other forms are also dependent upon specific toxic causes.

Whether syphilis is responsible for a proportion of the cases of acute myelitis is still an open question. The disease may develop during the first months of syphilitic infection, but how much the specific virus has to do in

causing the actual inflammation, an inflammation that has anatomically nothing "syphilitic" about it, cannot be decided.

There is still much discussion as to the pathogenesis of acute myelitis. Many believe that it is primarily an inflammatory process of the parenchyma, with coincident circulatory disturbances; others teach that the vascular phenomena are the primary ones, and the changes in the parenchyma and other constituents of the cord are coincident and secondary. The latter is the more reasonable view. Recently Tieten has endeavored to prove that emboli, often so small as not to be easily recognized, are the essential cause of acute myelitis. He thinks that his contention is supported by the fact that the lesion generally follows the line of the blood-vessels; in some cases the microscopic examination may show corresponding vascular changes. There is no doubt that occasionally acute myelitis develops in this way, but the great majority of cases do not.

When a spinal cord containing a single or a number of inflammatory foci is removed from the body, certain changes are apparent. Naturally the deviation from normal in the recent state will vary largely with the intensity, the extent, and the acuteness of the process. There may be considerable increase of cerebrospinal fluid. When the pia is exposed, there is seen more or less congestion of its blood-vessels, particularly over the affected segments. If the cord is laid on a flat surface and the finger carried lightly over it from the oblongata to the filum terminale, the area of softening will be quickly detected by loss of the resistant, elastic feel which the normal cord has, and by the presence of areas of a pultaceous, semiliquid consistency. Care is necessary not to confound liquefaction of a cord artificially produced during its removal, and cadaverous decomposition with areas of myelitis. When the cord is cut into segments with a razor, preparatory to hardening, difficulty will be at once experienced in making a clean cut through the softened area. The substance of the inflammatory area is nearly diffuent, and flows after the knife has passed through it. If the inflammation has been rapid and profound, the color of the destroyed tissue will be reddish white and the consistency almost fluid. A reddish-brown or chocolate-red appearance bespeaks hemorrhagic myelitis. If it has been of slow formation, the cord will be grayish white, with a slight reddish tinge, and of a semisolid consistency. On cross-section the normal markings and differentiation of the components of the cord cannot be made out.

The extent and confines of the lesion of acute myelitis are variable. It may be a single focus which extends through several spinal segments at different levels, in which the inflammatory process is of different degrees of severity and not symmetrically distributed. The area of softening may be confined to a single segment of the cord, or it may be diffuse and involve different constituents of different segments. Oftentimes, when areas of softening are multiple, some of them are so small that they can be detected only on microscopic examination. If it predominates in the central gray matter, it is known as central myelitis. It may extend throughout the larger part of the cord, constituting what is known as ascending and descending myelitis. It may occur in multiple foci (disseminated myelitis) or it may be confined to the gray matter (poliomyelitis). A differentiation between inflammatory and noninflammatory softening of the cord from anatomic considerations alone is impossible. Theoretically it is possible, by taking into consideration the genesis of the disease. When an agent capable of

exciting inflammation is the cause of the softening, it is naturally considered inflammatory.

It is very difficult to harden the affected segments for microscopic examination, and much information can be obtained from teased fresh specimens. In teased preparations, it will be seen that there is a profound disintegration of the substance of the cord. Leukocytes are numerous and intermingled with the *débris* of nerve-matter, such as free myelin-drops, the remains of myelin and axones, round granular cells, and fat-globules. Sections stained after Weigert's method show in the recently involved areas distended blood-vessels, accumulation of leukocytes in the perivascular spaces, and infiltration of the tissue with round granular cells (compound granule-cells). Small myelitic foci may be confined apparently to the area of distribution of an artery, but the larger ones do not have any evident relationship of this kind. The process of inflammation and destruction is most intense in the gray substance, because of the wealth of blood-vessels in this part. The vessels are overfilled with blood and much distended, especially the veins. The outer coat of the vessels is the seat of infiltration with cells of an epithelioid nature, or with red and white blood-corpuscles. In the vicinity of the vessels and in the vessel-walls themselves are clumps of pigment of hematogenous nature; hemorrhagic infiltration may take place. Oftentimes the inflamed area contains only blood-vessels, some connective tissue, and a homogeneous or granular detritus.

If the process of softening has not been very acute, the neuroglia-cells may show little change except that of tumefaction. Often, however, they suffer destruction coincidently with the parenchyma of the cord. If the focus of inflammation has been a slow and persistent one, the neuroglia and other sustentacular tissue of the cord may be increased and the nerve-tissue relatively diminished. This increase of neuroglia is a genuine glia proliferation, the result of karyokinesis.

The parenchyma of the cord suffers a decided change in the early stages of the inflammation, as has been determined experimentally. The most profound and striking change in the neurones is the swelling and disintegration of the Nissl bodies. The nerve-fibers are apparently thickened and tortuous, and, when seen on cross-section, seem of very different caliber; some of them are considerably enlarged, the medullary sheath closely adherent to the axis-cylinder and capable of staining only slightly with hematoxylin and carmin. Other axones are much smaller than normal. They have a peculiar crumpled appearance, and appear indistinctly granular. Naturally, if the inflammation is severe, the destruction of tissue may be so complete as to wipe out nearly all of the nerve-elements of a given focus. The large ganglion-cells do not suffer such complete destruction as in poliomyelitis, except when the inflammatory area implicates the ventral cornua; nevertheless, they are always altered to some degree. The substance of the cell-body presents a peculiar opacity or cloudiness; and this, with the indistinctness of the cell-nucleus and the disintegration and partial or complete disappearance of the Nissl granules, causes a homogeneity of the cell, to which the term hyaline swelling has been given. This condition is seen in the early stages of inflammation, and particularly when the process is not severe. Sections stained with methylene-blue after the method of Nissl show the conditions known as chromatolysis and plasmolysis, dependent upon the severity of the process. These changes of the ganglion-cells are

strictly comparable to those of acute hemorrhagic encephalitis. The axon may be tumefied and varicose, and the protoplasmic processes in various stages of decay, up to complete disappearance; in short, the intraspinal constituents of the peripheral neurone are in different stages of disorganization. Above and below the inflammatory focus areas of secondary degeneration are found extending a variable distance, depending upon the columns of the cord the continuity of which has been severed. Above the seat of the lesion the secondary changes are in the posterior columns of the ascending cerebellar and the anterolateral tracts; while below, they affect principally the pyramidal tracts, with very slight involvement of Burdach's column.

In peripheral myelitis caused by meningitis the infiltration may be regularly disseminated, occurring in little groups, or it may extend along prolongations of the pia into the cord. There are swelling and proliferation of the neuroglia, slight hemorrhages, and often infiltration and degeneration, by the meningeal exudate, of the nerve-roots that are implicated.

Myelitis from such condition as hydrophobia does not differ from other forms of myelitis, except by the degree of the intensity of the process. In cases recently studied, there have been found, in addition to hyperemia and hemorrhages, two kinds of inflammatory processes: One is characterized by profound vascular infiltration, especially in the gray matter, but also in the white, accompanied by leukocytic accumulation (the so-called rabic tubercles) along the course of the vessels toward the central canal. In the second form the vascular infiltration is much less pronounced, but the softening of the tissue is greater. The hemorrhages which result with this form of myelitis are due to rupture of vessels, and are found oftenest in the posterior horns and around the central canal. But they likewise occur in the anterior horns. The changes are not limited to the cord; they are to be found also in the oblongata.

The myelitis that occurs with gonorrhea is not well understood. It is a question whether the gonococcus itself causes the myelitis or meningomyelitis, or whether the changes in the cord are caused by a streptococcus the development of which the gonorrhea favors.¹ Possibly this form of myelitis is due to a toxin. The pathologic changes have recently been described by von Leyden, who found a more or less typical meningomyelitis. There was a fairly well-marked round-cell proliferation of the pia, swelling of the axones, a production of granular cells, but no hemorrhages or hyperemia.

Myelitis secondary to neuritis is characterized by tumefaction and destruction of the axones, hyperplasia of the neuroglia, degeneration of the ganglion-cells, thickening of the blood-vessels, and degeneration of the posterior roots. The changes in the spinal cord in one such case were traceable in Goll's column as far as the oblongata.

Associated with acute myelitis there are extensive changes in other organs, particularly the urinary, such as purulent cystitis, pyelitis, and pyelonephrosis.

In almost all cases of myelitis in which the cord is examined some considerable time after the inflammatory process has subsided, degenerative changes are found in the blood-vessels. It is not always possible to say whether such arterial degeneration is the result of the primary causes of the

¹ It is not at all improbable that the gonococcus has been mistaken, in cases of this sort, for the *Diplococcus intracellularis meningitidis*, to which it bears a striking morphologic resemblance.

inflammation, or whether it is not coincident with the reparative process of neuroglia and connective-tissue increase. When connective tissue forms, it has all the characteristics of scar-tissues; and as one of these is a persistent tendency to contract, such contraction may materially interfere with the function and nutrition of the vessel.

Cases that come to postmortem examination in a comparatively short time after the onset of the disease do not show any of these reparative processes; the lesion in such cases is a destructive one pure and simple.

Syphilitic Myelitis.—Some writers are unwilling to admit the existence of acute syphilitic myelitis apart from a meningomyelitis or a gummatous myelitis. Although the morbid changes constituting the myelitis that occurs suddenly in the first years after syphilitic infection have nothing absolutely pathognomonic about them, yet no one can deny its occurrence nor doubt its dependence upon syphilis. The pathologic features of the lesion are not very different from those of other forms of myelitis, and consist of multiple foci of inflammatory and edematous softening, some small and isolated, others large and confluent, associated with striking inflammatory changes in the blood-vessels, leading to endarteritis, endophlebitis, and minute hemorrhages. The tissue surrounding the affected vessels is infiltrated with leukocytes, there is destruction of ganglion-cells if the inflammatory foci are in the gray matter, and destruction of the white matter if the process is essentially a leukomyelitis. The usual secondary degenerations, ascending and descending, can be traced from the destructive process. The greater the interval between the beginning of the lesion and the examination, the greater will be the amount of neuroglia present. In these cases the meninges may be entirely spared; but, as a rule, they are somewhat involved, particularly the pia at the level of the myelitic area. The pia is infiltrated and thickened by round-cell infiltration. This meningitis is not primary, but secondary to the inflammatory process in the cord.

Purulent Myelitis.—Purulent myelitis or abscess of the cord is a rare condition; it occasionally occurs as a process secondary to bronchiectasis, to purulent affections of the urogenital apparatus, to dysentery followed by abscess of the liver, and to metastatic meningitis. The seat of the most destructive changes is almost invariably central. In such a focus the nerve-tissue is replaced by a mass of pus and detritus of nerve substance. Around the abscess-cavity there is found an area of diffuse myelitis, which may extend to the periphery of the cord, particularly in those cases in which an abscess is secondary to meningitis. The histologic changes in the area surrounding abscess of the cord do not differ particularly from those of ordinary acute myelitis. They consist of swelling of the axis-cylinders, degeneration of nerve-fibers, and of granule formation and infiltration of the surrounding tissue with round cells.

The location of spinal abscesses in the center of the cord is analogous to that of the brain-abscesses that develop with epidemic cerebrospinal meningitis. The pyogenic factors are brought in through the vessels which pass from the periphery toward the center. The structures at the center of the cord are less compact than at any other part, and this gives more space for the accumulation of pus.

On the dying-out of the pyogenic agents, the pus and detritus may be absorbed and more or less glia-tissue produced, but *the ganglion-cells are not*

regenerated. The increase of neuroglia constitutes a sclerosis, and the amount of this depends largely upon the character, the seat, and the intensity of the inflammation. The increase of neuroglia-tissue is most pronounced when the inflammation is not so acutely destructive. If vascular changes are marked and the destruction of tissue great, consecutive increase of neuroglia-tissue will be comparatively slight and the reparative new growth will be mainly made up of connective tissue. The appearance, extent, and structure of a sclerosed area will vary somewhat with each case, and especially with the time that elapses between the occurrence of the original lesion and the post-mortem examination. Often it is so conspicuous that it is readily recognized with the naked eye and by the touch. It forms grayish-white areas which may extend across the entire segment of the cord, or they may be limited to certain parts and seen in different levels. This new formation undergoes contraction and retraction like every scar-tissue. Occasionally the sclerosed area undergoes secondary changes, apparently the result of insufficient nutrition, and the consequences are manifest in a variety of softening which is termed gray gelatinous degeneration.

Instances occur in which the reparative process is mainly of connective-tissue growth, not only in purulent inflammation of the cord, but in cases of poliomyelitis and in other severe lesions. The connective tissue arises from the intramedullary prolongations of the pia and from the adventitial sheaths of the blood-vessels. Its appearance to the naked eye is similar to that of true sclerosis or increase of glia-tissue; but on microscopic examination the feltwork formed by the interlacement of the glia prolongations is absent, as are also the so-called cell-bodies of the glia-cells. On the other hand, the newly formed connective tissue, the result of round-cell proliferation, is easily recognized.

In purulent myelitis or abscess of the spinal cord, this newly formed connective tissue is in the shape of a capsule around the purulent focus. Its formation is exactly similar to that of any pyogenic limiting membrane. When the purulent myelitis occurs in little foci, the pus may be absorbed, and minute patches of connective tissue will remain to indicate its previous location.

Tuberculous Myelitis.—Tuberculosis of the spinal cord is an uncommon lesion. It may be of the meninges and the cord, constituting a tuberculous meningomyelitis, the most frequent variety, or it may occur in the form of solitary or multiple tubercles. The first form develops from tuberculous invasion of the spinal pia, and implicates the peripheral part of the cord. In this, small tubercles form which confine themselves narrowly to the prolongations and vessels of the pia; or it causes a vascular infiltration tending to focal or diffuse myelitis, without nodule formation.

The tubercle bacilli may invade the substance of the spinal cord and cause cell proliferation and tissue destruction terminating in necrosis; in short, a destructive myelitis, without previous or coexistent disease of the spinal pia. In these cases there is commonly, but not necessarily, tuberculosis in other parts of the body. A case of tuberculous myelitis, in which there were no other manifestations of tuberculosis, has recently been recorded by the writer. In a case of amyotrophic lateral sclerosis reported by Dana and the writer, there was found, in addition to the lesions common to this disease, a softening of the spinal cord, extending from the level of the first dorsal to the third cervical segment, was found. On microscopic examina-

tion the necrosis was seen to extend lower in the cord than was apparent to the naked eye, gradually disappearing in the third dorsal segment. The necrosis was not accompanied by any hemorrhagic process, and there was but slight inflammatory reaction. Bacteriologic examination revealed the presence of tubercle bacilli.

Solitary or multiple tubercles may be found in the spinal medulla, oftener in the gray than in the white substance, and this evidence of tuberculosis may be the only one found in the body. This is exceptional, however.

The pathogenesis and the histologic structure of solitary or multiple tubercles of the spinal cord are the same as those of similar conditions in the brain. The accompanying lesions of the cord are those of subacute myelitis, with destruction of tissue and secondary degeneration. This is in contrast to the lesions of the cord produced by the infiltrating variety, the diffuse nodular form, or these two combined, in which the anatomic changes are



FIG. 181.—Tuberculosis of the spinal cord.

more those of acute myelitis, viz.: leukocytic infiltration of the pia; distention of the blood-vessels and infiltration of their walls; excess of glia-nuclei in the white and gray substance; infiltration and perivascular exudation of the medullary vessels, more predominant in one tract or column than in another; neuroglia proliferation, especially around the central canal; small tubercles constituted of epithelioid cells and leukocytes, the latter especially at the periphery; and degeneration commensurate with the implication and the seat of the lesion.

Syphilis of the Spinal Cord.—Syphilis of the spinal cord may involve the meninges, especially the pia, the blood-vessels, and the substance of the cord, and possibly its injurious influence may be limited to effects upon the ganglion-cells. The most common lesion of the spinal cord due to syphilis is that of meningomyelitis, the brunt of the process being borne by the meninges and the blood-vessels. Syphilitic disease of the cord is

almost always associated with similar manifestations in the brain, although the latter may be inconsequential compared to the former.

The disease of the blood-vessels is not so typical as that in the cerebral vessels, and is easily confounded with the arteritis accompanying tuberculosis and sarcomatosis; and for this reason it is often difficult to say whether the vascular change in a given specimen is syphilitic or not, especially when other manifestations of syphilis of the cord are absent.

The cell proliferation may be confined to a circumscribed area or it may be diffuse. In the latter case one portion may be in a state of retrogressive metamorphosis and another in a state of active proliferation. In rare instances the veins are affected more severely than the arteries, the lesion being practically a phlebitis obliterans.

Whenever the changes take place they have a tendency to lead either to an obliteration of the blood-vessel, with or without thrombosis and subsequent softening; or to thinning of the vessel walls leading to aneurysm or rupture. In addition to this form of syphilis of the blood-vessels, there may occur typical gummatous arteritis, the histology of which does not call for special description. The arteries of the pia are particularly prone to this sort of involvement, secondary to gummatous foci of the pia.

Meningomyelitis of syphilitic origin is not an uncommon disease of the spinal cord, especially of the cervical and dorsal portions. It is impossible to tell from examination of the completed process whether the disease began originally in the pia or whether there was primarily syphilitic disease of the intramedullary connective tissue with extension to the pia. In extent and distribution the lesion is by no means sharply circumscribed, although circumscribed softening similar to that occurring in the brain with syphilitic arteritis has been observed. The pia may be the seat of diffused or circumscribed gummatous formations. The pathologic changes in the pia are the same as those of cerebral syphilitic leptomeningitis. The pia is much thickened and adherent to the periphery of the cord, from which it is detached at the expense of considerable tearing and laceration of the latter. To the touch and to the naked eye it may have lost all its normal features, and in its place is found a tough, resistant, grayish-white membrane; or it may be in different stages of degeneration and caseous transformation. The thickness of the pia may vary much. In one area it is as thick as the thumbnail; in another only a slight, round-cell infiltration is present. The dura may be entirely spared, or it may have undergone similar changes to the pia and be adherent to the latter. The accompanying and consecutive changes in the cord are usually shown by whiteness of the peripheral portions of the cord. Examination with the microscope shows that the degeneration of the periphery is secondary to a proliferation and overgrowth of the connective-tissue septa and to compression by the adherent meninges. There are almost always associated with it a degree of syphilitic disease of the arteries and veins of the cord, and a round-cell infiltration of the capillaries. There may be swelling and degeneration of the nerve-fibers, and the formation of fat-globules in the myelin-sheaths, and some increase in the amount of neuroglia. Secondary degeneration occurs; its extent and distribution will depend upon the conducting fibers whose continuity has been interrupted.

A considerable number of patients who have had syphilis develop in a shorter or longer time after the inception of the disease a rather well-defined

complex of symptoms, motor and sensory, the former predominating, referable to the lower extremities and to the pelvic viscera. Erb and some of his disciples have described this condition under the title of syphilitic spinal paralysis. The lesions found after death are essentially those of transverse myelitis, predominantly in the lower dorsal cord, with a special tendency to involvement of the lateral column and associated with syphilitic endarteritis.

In rare instances leptomeningitis or meningomyelitis has its starting-point in the vertebral column. Sequentially to this there occurs thickening of the pia, which crowds itself backward into the anterior and anterolateral portions of the cord, accompanied by round-cell proliferation and degeneration in the coats of the blood-vessels. The microscopic features are those of a meningomyelitis. The remarkable feature in a few cases of this kind that have been reported is that the dura remains uninvolved. It is thought, therefore, that the involvement of the pia and of the parenchyma of the cord takes place through the vascular system.

Primary syphilitic spinal pachymeningitis is much rarer than cerebral syphilitic pachymeningitis. A form of syphilitic dural involvement to which Charcot and Joffrey gave the name pachymeningitis cervicalis hypertrophica is of infrequent occurrence. The thickened dura forms an annular sheath around the cervical cord and causes compression of it. On the outside the dura is adherent to the vertebræ and internally with the pia, and it is impossible to separate one from the other. The hypertrophic state of the dura is due essentially to new formation in its outer and inner layers.

The spinal roots may be implicated in syphilitic meningitis. They may suffer compression from meningeal encroachment or there may be peri- and endo-neural infiltration with subsequent decay of the nerve-fibers. The spinal roots are rarely involved alone as the single evidence of intraspinal syphilis, although it should be mentioned that Kaleler has described a multiple syphilitic root neuritis.

Circumscribed gummatous formations may develop in the meninges of the cord the same as in the intracranial cavity, but circumscribed gummatous formation of the spinal cord substance is rare.

Although there have been a number of cases of chronic anterior poliomyelitis observed in which syphilis was the only attributable cause, and in which noteworthy amelioration of the symptoms occurred while the patient was undergoing antisymphilitic treatment, a study of the morbid anatomy of these cases has not enabled us to say with anything approaching certainty that there is a syphilitic form of this disease. In the cases in which syphilis has been looked upon as a causative factor there have been found the pathologic changes common to the ordinary form of chronic anterior poliomyelitis, such as diminution in number of the ganglion-cells of the anterior horn and atrophy, and vacuolation of the remaining cells, and especially shrinkage of their nuclei and protoplasmic processes associated with degeneration of the peripheral nerves.

Chronic Myelitis.—In reality, chronic myelitis might include nearly all forms of sclerosis of the cord. Here the term will be used in a restricted sense, to signify degeneration of the spinal cord conforming in outline to acute myelitis. Chronic myelitis may be the sequence of an acute or subacute myelitis, and, like it, may be focal, disseminated, or diffuse, and at any level of the cord. When such lesions occur, they of course produce

secondary degeneration, and these secondary degenerations may apparently be of the systematized variety.

No complete description of the pathologic changes of chronic myelitis can be given; for the lesions constituting the disease, and those the immediate result of it, vary with almost every case, and depend upon the intensity, the seat, and the extent of the lesion. It may, however, be said that there are nearly always striking macroscopic and microscopic changes. In the usual case of chronic transverse myelitis the cord is smaller, somewhat shrunken at the level in which the degeneration is most marked, and of an increased consistency. If the disease process is of long duration, there are accompanying atrophic and degenerative changes in the spinal meninges and extramedullary blood-vessels. The white matter loses its normal pale color and is of a grayish tint, while the gray matter is of a slaty color. These alterations, with the increased resistance which the degenerated area offers to the passage of the knife on making sections of the spinal cord, are the only gross features of any importance, except that the pia may be adherent to the cord and offer resistance to its removal. On microscopic examination the degeneration of the neural elements and the increase of the supporting elements are very striking, the affected areas staining deeply with those stains, such as carmin, which are taken up by new tissue. The amount of destruction of the parenchyma corresponds, in a measure, to the amount of connective-tissue new formation and the degree of degeneration of the blood-vessels. In some cases the degenerated area forms a ring around the spinal cord, and is then known as annular sclerosis; in other cases the lesions are irregularly distributed, involving no particular set or tracts of fibers, but producing secondary degeneration of those which happen to be involved. To these cases the designation disseminated myelitis is often given. The changes in the blood-vessels are those of ordinary degeneration, and do not call for special description.

The lesion of the ganglion-cells is that of chronic parenchymatous degeneration and progressive atrophy. The more noxious the cause of the myelitis has been, the more rapidly destructive will be the process in the cells. Sclerotic areas have a decided predilection for the white matter, and not infrequently the changes in the gray matter are comparatively slight.

The supporting substance of the spinal cord, the neuroglia, and the connective-tissue meshes carried into the cord by the pia and the blood-vessels, are the seat of well-marked proliferative and degenerative changes.

Poliomyelitis; Inflammation of the Gray Matter of the Spinal Cord.—**Acute Anterior Poliomyelitis.**—Anterior poliomyelitis is a disease characterized pathologically by inflammation of the ventral gray matter of the spinal cord. It occurs with such preponderating frequency in children that it is often spoken of as essential paralysis of children. Experience of latter years has demonstrated that it occurs oftener in adult life than was formerly supposed. Anterior poliomyelitis was put on a firm anatomic basis by the labors of Pierret, Charcot, Gombault, Roger, Damaschino, and others. The disease does not often lead to death, and therefore opportunity is rarely had to examine the immediate lesions. Until 1883, no recent cases had come to autopsy; but in that year Archambault and Damaschino made a careful histologic examination of the spinal cord of a child who had died from an intercurrent attack of bronchopneumonia twenty-six days after the beginning of the poliomyelitis. During

the last ten years, a number of recent cases have been examined in which modern technic has been utilized. The records of such cases have been of great service in establishing the early morbid changes.

There can be little doubt that acute anterior poliomyelitis is an infectious disease. Its occurrence with or after infections, its clinical manifestations and course, its termination, its prevalence in epidemic form, its recurrence at certain seasons, and its morbid anatomic accompaniments, all point to the truth of this statement. No specific organism has yet been isolated in any example of the disease. In one case the Weichselbaum-Jaeger diplococcus was found in the fluid of the lumbar puncture. The lesions of anterior poliomyelitis do not confine themselves strictly in every case to the anterior horns; nevertheless, this part of the spinal cord bears the brunt of the attack. It will be recalled that the ventral cornua of the spinal cord are made up of ganglion-cells, their processes, neuraxones, and their terminations; of neuroglia, and of blood-vessels and lymph-vessels and connective-tissue stroma. It is believed by some that the process begins in the ectodermal elements, while others think that the mesodermal are primarily involved. Be that as it may, it is necessary, in order to understand the distribution of the lesion, that a clear comprehension is had of the structure of the anterior-horn cells and their vascular supply. The cells of the ventral horns of the spinal cord are bipolar or multipolar nucleated masses of protoplasm, that form the beginning of the peripheral system of motor neurones. Each cell consists of a nucleus and a nucleolus; the Nissl bodies; the achromatic substance, composing the greater portion of the cell-body; the protoplasmic processes and their gemmules; and the neuraxones, their collaterals and terminal arborizations. These axones go out from the anterior gray matter as the intramedullary roots of the anterior spinal nerves. They then pass toward the posterior spinal ganglia, thence to the periphery, where they eventually terminate in arborizations. They are inclosed in the same sheaths with the sensory nerves. The other important neural element of the ventral horns is the arborization of some of the central motor neurones which have come down from the brain as the pyramidal tracts. All of these undergo alteration in variable degree in anterior poliomyelitis.

The distribution and extent of the inflammatory process depends upon the arterial supply of the gray matter and the intensity of the infection. The principal artery of the ventral portion of the spinal cord is the anterior spinal artery, formed by the two descending branches of the vertebral. From it arise the central arteries which pass backward into the anterior median fissure. When they reach the bottom of the fissure, they bend toward the right or the left and pass to the central part of the gray column. Here they divide into ascending and posterior branches. At first the fine branches take a somewhat horizontal course; most of them break up into arterioles in the vicinity of branches of other central arteries which lie deep in the substance of the gray matter. In cross-section of the spinal cord, one sees, therefore, that the gray matter is supplied by two or more central arteries. It is believed that the blood-supply of any certain group of ganglion-cells is not dependent upon an individual artery or its branches, but that each arterial branch is distributed to more than one group of ganglion-cells. And it has been found that the gray cornua and the adjacent portion of the white matter are supplied in common from the central and peripheral arteries.

Formerly it was taught that the essential lesion of acute anterior poliomyelitis was a primary inflammation of the ganglion-cells; but at the present time it is generally accepted that the pathogenic agent acts primarily on the blood-vessels, and secondarily on the ganglion-cells.

A spinal cord the seat of a recent acute anterior poliomyelitis shows the pial coverings congested, particularly over those areas which are the seat of



FIG. 182.—Chronic anterior poliomyelitis.

inflammation. In addition, there is considerable increase of subpial fluid. When the cord is laid upon the dorsal surface and the finger passed lightly



FIG. 183.—Chronic anterior poliomyelitis (author's collection).

over the ventral surface, some area, most likely in the cervical or lumbar enlargement, is less resistant to the touch than other portions. The anterior spinal artery and its anterior fissural branch are congested. The focus of inflammation may be slight or extensive, single or multiple. In general the entire gray matter on section is more vascular than normal, and is often the

seat of a red softening. With the naked eye, and much more distinctly with a magnifying glass, it is seen that one anterior horn is more involved than the other.

Specimens hardened in alcohol or formaldehyd and stained with methylene-blue show striking changes in the blood-vessels and in the cells of the anterior horns. The most important lesion, however, is the series of changes in the nerve-cells. The changes vary from insignificant peripheral or central chromatolysis, plasmolysis or disintegration of the achromatic substance, homogeneous transformation, and vacuolation, to complete reduction of all of the constituents of the cell, so that only *débris* remains of the cells that bore the brunt of the inflammatory process. Many cells are shrunken, of deformed outline with dislocated or disintegrated nuclei, the cell-body showing partial or complete dispersion of the chromophilic substance. Many of the disintegrated cells are completely surrounded with round cells. This round-cell infiltration can be taken as an index of the intensity of the inflammation. Only a small proportion of the cells that remain are of normal size. Some of them are enlarged, shapeless, swollen, and apparently devoid of nuclei. Others are shrunken, without detectable processes except a thickened, varicose axone. Although different cell-groups suffer in different cases, no group is especially predisposed to involvement. The blood-vessels of the pia and the cord are usually found distended with blood, the walls thickened, due principally to a proliferation of the connective tissue in the sheaths. The perivascular spaces are enlarged and infiltrated with round cells. In severe cases punctate hemorrhages have been found. Even with the Nissl stain the change in contour of the ventral cornua is very apparent.

Sections hardened in Muller's fluid and stained with carmin or aluminohematoxylin show the focus of inflammatory softening with great distinctness. Usually the antero-external portion of the diseased anterior horn is the seat of the most severe lesion; and often the adjacent white matter, the anterior lateral tracts, and very rarely the posterior columns, are somewhat affected. There is a marked cellular proliferation in and around the walls of the blood-vessels, especially in the larger branches; the lumen of the vessels is distended with corpuscles, and here and there are hemorrhages of varying size in the course of the arteries. The alteration of the ganglion-cells is less striking than in the methylene-blue section; but even with carmin stain the nuclei are not recognizable, the prolongations are lost or stunted, and the body of the cells has undergone granular degeneration. The nonmedullated fibers of the anterior horns are swollen; and sections stained with Mallory or Weigert neuroglia-stain show that the glia substance is greatly increased where complete destruction has not taken place. Often an entire ventral cornu, or the segment of it that is the seat of the lesion, is reduced to a homogeneous mass, the only elements to be made out being the diseased blood-vessels and a few fibers of supporting tissue, with here and there nerve-fibers in various stages of destruction. In other words, a genuine coagulation necrosis has taken place in the ventral cornu. The contour of the horn is not materially changed in recent cases, but some of the axones passing out to form the anterior root-nerves are swollen, others shrunken and twisted, while yet others appear as if they had been subjected to severe compression. The white matter bordering on the inflammatory area, the anterolateral column, is the seat of a variable degree of acute inflammatory softening, with similar, though less marked, vascular changes.

The inflammatory focus in which the alterations are most profound extends through one or more spinal segments. It is commonly situated either in the lumbar or the cervical enlargement. The lesion may be very extensive; even the nuclei of the oblongata may be involved. The peripheral nerves and the muscles to which they are distributed undergo acute degeneration.

In old cases of poliomyelitis the cord shows an appreciable diminution in outline anteriorly on the side corresponding to the lesion, and the emerging anterior root-fibers are diminished in number and size. There are no vascular changes of any importance. When the spinal cord is divided, the seat of the lesion, generally one of the enlargements of the cord, becomes evident to the naked eye on account of the shrunken outline of the anterior horn; in some cases this is so pronounced that there seems to be an absence of the anterior cornu on the diseased side. Sections hardened in Müller's fluid and stained according to Weigert's method show this deformity of the cornu in the most striking manner. The atrophic anterior horn is seen to consist of a rarefied network of fibers which is apparently due to an increase of the neuroglia and of the connective tissue; the cells of Deiter, or astrocytes, are present to a considerable degree. The nerve-fibers of the anterior horn are almost completely absent, the blood-vessels are thickened, their lumen is distended, and the perivascular spaces are enlarged. In short, there is formed a gray sclerotic patch, within which the neural constituents have perished to a more or less complete degree. Often there is a relative increase of the glia and connective tissue and corresponding diminution of axones in the antero-external columns. This does not, however, usually reach any considerable degree. The roots of the anterior spinal nerves from the anterior horns are delicate, slender, and degenerated, and the anterior commissure appears poor in fibers.

Sections stained with carmin or with methylene-blue reveal a striking absence of ganglion-cells and degeneration of those remaining. The cells of the anterior cornua are not destroyed in a uniform manner. Certain cell-groups are found involved with remarkable constancy, while others, and particularly the column of cells situated toward the apex of the anterior cornua internally and which give origin to the nerves of the muscles of the back, are frequently spared. Unless the whole anterior horn is destroyed, this group of cells is generally found in fairly healthy condition. Aside from this, the other cell-groups may be represented only by single or a few shrunken, atrophic, pigmented, granular masses of protoplasm. With the Nissl stain the axones and protoplasmic processes can be traced but a short distance from the cells that remain.

The blood-vessels, and particularly those around the degenerated cells, are the seat of degenerations already mentioned. Their caliber is enlarged and their walls thickened. The walls of the central artery of the longitudinal sulcus are usually distinctly degenerated. In many sections large spaces representing the place from which degenerate vessels have dropped out in the preparation of the specimen, and the distended perivascular spaces, are to be seen; while in the walls of the vessels remaining little heaps of pigment are seen.

Distribution of the Lesion.—The lesion is almost always confined to one side of the cord; in rare instances, corresponding to the clinical distribution of the symptoms, both sides of the cord are involved, although this may be

seen in different segments. The cord in the vicinity of the cervicodorsal region, or the dorsolumbar, is usually the seat of the lesion, the latter oftener than the former.

In addition to the changes already described, there are other deviations from normal, not only in the spinal cord, but in the brain and in the peripheral nerves; these are predominantly secondary manifestations. In some cases of long standing the entire half of the cord of the involved segment is distinctly smaller than the healthy side, and, although it is most uncommon to find any changes in the white columns other than those already mentioned, it is not so very uncommon to find that the posterior horn is considerably shrunken and that the cells of Clarke's column are atrophic. This condition bespeaks participation of these structures in the remotely anterior inflammatory process. These changes may, however, be explained on the ground of arrested development in these parts, on account of the destruction of a certain number of cells and fibers, and to a degeneration or ascending atrophy similar to that which goes on in the spinal cord after amputation of an extremity. The coexisting alterations in the brain are confined to the motor regions of the cortex opposite to the side paralyzed. This is by no means a common condition, but it has recently been found in a case carefully examined with this end in view.

The changes that occur in the roots of the anterior spinal nerve have already been spoken of, and those to be found in the trunks of the mixed nerves correspond to them. Naturally, if the cell-body is destroyed, the neuraxone and its termination will suffer destruction. In recent cases there will be a marked descending neuritis, while in old cases there will be more or less complete degeneration of the neuraxone. As the ganglion-cells of the anterior horns are the trophic centers for the muscles, it is natural that commensurate alteration will be found in the latter. The process that goes on in the muscles is essentially one of degeneration, with interstitial lipomatosis and even complete disappearance of the muscular fibers. Not alone the muscles of the atrophic limb undergo pathologic changes, but the bones, blood-vessels, and other constituents of the extremity as well. The surface of the bones is smooth and devoid of roughenings for muscular attachments. On cross-section the central canals and the Haversian spaces are diminished in size, while the lacunæ are correspondingly increased. The walls of the blood-vessels are thin, their caliber diminished, and the perivascular lymph-spaces are distended and gaping.

It has long been recognized that a previous anterior poliomyelitis is followed by a form of progressive muscular atrophy, often similar in its distribution to that of the Aran-Duchenne type. In such cases the lesion of the latter condition has been found adjacent to that of poliomyelitis.

Marinesco has described a condition of chronic poliomyelitis of ischemic origin occurring in adults, in which the lesions consist of small areas of hyperplasia of glia-tissue surrounding open spaces. He believes that this formation is the result of changes in the blood-vessels, which lead to more or less complete obliteration of the lumen. Often this process is associated with sclerosis of the posterior columns and tabic muscular atrophy.

The pathogenesis of subacute and chronic poliomyelitis is by no means the same in every case. In one class of cases the morbid conditions are very similar to those of acute poliomyelitis. In other words, there is a vascular disease of the ventral horns, with parenchymatous degeneration.

The inflammation may be confined to definitely limited foci or to a single focus. Within this area the ganglion-cells are in different stages of destruction, showing changes quite analogous to those in the cells of acute poliomyelitis. In later stages the remains of the inflammatory process are seen in a sclerosis of the ventral horns or in diffuse inflammatory changes.

In another class of cases there is a diffuse, widespread atrophy of the cells of the ventral cornua, often associated with slight changes of an interstitial nature in the white columns of the cord, microscopic examination revealing no positive evidence of previous inflammation, either in the blood-vessels or in the parenchyma. In fact, the lesion is practically similar to that found in spinal progressive muscular atrophy or in amyotrophic lateral sclerosis, except that changes in the pyramidal tract are absent. In both instances the entire peripheral motor neurones are degenerated, and likewise the muscles to which they are distributed.

Acute Ascending Paralysis (Landry's Paralysis).—Toxic or Infectious Processes in the Peripheral Motor Neurones.—Some such name as this must be chosen to describe the morbid conditions on which are dependent a number of well-defined, easily recognized groups of symptoms, the most typical of which is known as acute ascending paralysis or Landry's paralysis. This disease is characterized clinically by the occurrence of paralysis developing (usually) from below upward, and leading to death within a short time through involvement of the bulbar nuclei. The absence of marked sensory symptoms and the preservation of irritability of the paralyzed parts to the faradic current are common clinical features.

The morbid anatomy of the disease has been the subject of much discussion. Some writers corroborate Landry, and find no changes in the central and peripheral nervous system; others describe extensive lesions in the central nervous system; while a third class, greater by far than the other two, finds lesions of the peripheral motor neurone that are held accountable for the disease.

The truth is, that acute ascending paralysis is an acute parenchymatous degeneration, of toxic-infectious origin, of peripheral motor neurones. The lesions in one case may be most striking, constituting an acute poliomyelitis, characterized by an acute exudative inflammation, with attending vascular lesion and subsequent ganglion-cell destruction, of the nature of an acute parenchymatous degeneration. The lesions of the ganglion-cell in and around the foci of exudative inflammation vary in different stages and degrees of chromatolysis and plasmolysis, irregularities of cell-outline, rupture of processes, and dislocation and destruction of the nucleus. Or there may be an exudative inflammation of the connective-tissue constituents of the peripheral nerves, and this may be of a hemorrhagic or even of a purulent nature and cause rapid destruction of the parenchyma. The nature of the poison can only be conjectured. Judging from the character and dissemination of the morbid changes throughout the entire system, it is probable that the disease is the result of some chemical toxin rather than the direct result of a specific organism; although in the exudation of a few cases organisms, such as *Staphylococcus pyogenes aureus* and *Streptococcus pyogenes*, have been found. Remlinger claims to have produced the disease in rabbits by inoculation with pathogenic cocci, and Rendu has seen symptoms of the disease follow inoculation of antirabic serum. The results of bacteriologic examination tend to show that the disease is due to infection,

but not always the same infection. The coexisting morbid changes in other parts of the body, particularly of the viscera, such as the spleen, the liver, and kidney, point out the severity of the general systemic infection. In almost every case in which microscopic examination has been made, there have been found acute splenitis and acute degeneration of the kidney.

It would seem that clinically two forms of the disease are recognizable, and that the disease is not necessarily a fatal one. In one instance the lesion is primarily of the cord and oblongata; in the other it is a neuritis with consecutive involvement of the cord. It is questionable if any case of acute ascending paralysis exists in which some anatomic lesion cannot be found by the aid of modern histologic technic.

PRIMARY SYSTEMIC DISEASES OF THE SPINAL CORD.

One of the most obscure questions in the pathologic anatomy of the spinal cord to-day is that of the primary systemic degenerations. In these diseases the pathologic process is limited to certain tracts or systems of fibers, wherein it may be followed throughout a great extent of their course. When two or more fiber-tracts of different function are involved, the disease is spoken of as a combined system disease. The number of cases of genuine systemic diseases of the spinal cord is not large.

Two or more systems of fibers of the cord may undergo primary degeneration coincidently and from the same cause. Such conditions are found in general paralysis, in Friedreich's disease, and in the disease that is known clinically as ataxic paraplegia and anatomically as combined lateral and posterior sclerosis. A transverse myelitis, by severing nerve-fibers from their trophic centers, may cause ascending and descending degenerations; and such degenerations may in some instances, during certain periods of their course at least, be strictly systemic. Such *secondary* degenerations, even though the lesions confine themselves to systems, should not be considered systemic diseases. Disease of certain tracts of fibers, such as the lateral columns, may result from leptomeningitis and multiple sclerosis. Such involvement may be, but is not necessarily, strictly limited to systems.

Whether the symptom-complex described under the name of ataxic paraplegia, or combined lateral and posterior sclerosis, is to be considered a strictly systemic disease is impossible to say at present. The lesions in cases of this nature are those of an associated involvement of the posterior and lateral columns, and particularly of the posterior columns and the crossed pyramidal tract. The involvement of the posterior columns is most pronounced in the postero-internal column and in the dorsal field of the postero-external column, and particularly in the dorsal region. The sclerosis of the lateral areas, although most common in the crossed pyramidal tract, frequently involves the direct cerebellar tract, the column of Gowers, and the lateral limiting layer. This is well shown by Fig. 184. It is usually said that the gray matter is uninvolved in this disease, but in the cord from which Fig. 184 was prepared there was degeneration in the cells of Clarke's column and of the fine white fibers of the anterior horns.

The degeneration seems to be primary. There is no increase of neuroglia; neither is there primary disease of the meninges nor of the vascular and perivascular structures, although in the terminal stages of the disease quite

pronounced vascular changes exist, with some increase of neuroglia. But these are secondary to the primary changes in nerve-fibers.

Primary Lateral Sclerosis.—The disease known as primary lateral sclerosis is an isolated primary degeneration of the lateral columns of the

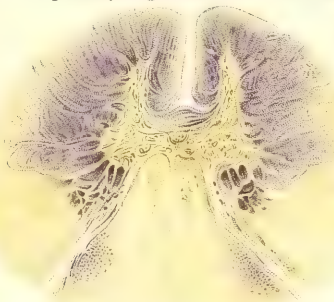


FIG. 184.—Combined posterior and lateral sclerosis (author's collection).

cord. There are those, however, who are unwilling to admit that it is a primary disease, claiming that there must be changes in other parts of the central nervous system upon which the spinal-cord lesion depends. The majority of cases of primary lateral sclerosis recorded have shown changes in other parts of the spinal cord, although in a few cases these were insignificant. Strümpell has reported a case in which no other lesion except that of the pyramidal tract existed. There were slight beginning changes in the cells of the anterior cornua. It is not contrary to our present conception of the histologic unit of the nervous system, the neurone, to believe that the terminations of the primary motor neurones should degenerate first at their peripheral distribution and extend gradually in a central direction. The point of termination of the central neuraxones is in the anterior horns around the ganglion-cells; and as the fibers lose their medullary sheaths on passing into the gray matter of the anterior horns, the degeneration of the intracornual axones is not revealed by the myelin stains.

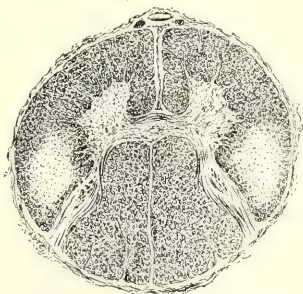


FIG. 185.—Primary lateral sclerosis (author's collection).

The histologic appearances of degeneration in the lateral columns of the cord do not differ from those found in combined system diseases. The area of degeneration may outline the crossed pyramidal tract with mathematic accuracy. It is not often, however, that the degenerative process is so sharply limited. Frequently it involves the anterolateral ascending bundle

or the lateral limiting layer; and the direct cerebellar tract and the posterior vesicular columns may be involved as well. The degeneration is that of primary sclerosis with partial or complete disappearance of the nerves and overgrowth of connective tissue with thickening of the vessel-walls.

The degeneration may extend throughout the entire pyramidal tract, or it may be limited to a few segments of the cord. In a few instances there has been found an annular myelitis associated with the lateral sclerosis; in other cases the anatomic picture was that of disseminated sclerosis.

Amyotrophic Lateral Sclerosis.—The principal lesion of amyotrophic lateral sclerosis is, as the name implies, in the gray matter of the ventral horns and the lateral white columns, but any portion of the entire motor system may be affected. When Charcot first described amyotrophic lateral sclerosis in the early '70's, it was as a type of systemic disease, the degeneration being situated in the pyramidal tracts and followed by atrophy of the large cells of the ventral horns and of certain groups of cells of the oblongata. The changes in the gray matter of the spinal cord and in the peripheral nerves were considered secondary. This view was advocated by Erb, and through his writings and teachings it has become widely disseminated. Many clinicians and pathologists (Gowers, von Leyden, Dana, and others) have been unwilling to accept this view; they classify the disease as a form of progressive muscular atrophy, regarding the changes in the peripheral motor neurone as primary, those in the central motor neurone as secondary or coincident. Neither of these two views is wholly satisfactory. We are ignorant of the causation of amyotrophic lateral sclerosis. Whatever the pathogenic agent is, it is one that acts slowly; for the disease nearly always progresses slowly, and the lesions produced are of a primarily degenerative type.

The writer leans to the former, and believes that the weight of evidence indicates that the disease in the beginning affects principally the terminals of the central motor neurone, and that the involvement of the peripheral motor neurone is secondary in point of time. There is no doubt that in many cases the clinical symptoms of involvement of the pyramidal tract antedate considerably those indicating involvement of the ventral horns. Neither is there any doubt that in the majority of cases the process of degeneration in the pyramidal tracts is in a more advanced stage, when opportunity is given to investigate the cord, than in the ventral cornua. In fact, the destruction is often complete in the former and still progressive in the latter at the time of death. It has been mentioned that the occurrence of primary degenerations of the pyramidal tracts has been doubted; but recently, as already mentioned, Strümpell has investigated a case in the spinal cord of which there was a striking degeneration of the pyramidal tracts, extending from the internal capsule to the lumbar cord. The motor neurocytes were regarded intact, no changes being revealed by the methods of investigation employed. There was beginning degeneration in the ventral horns at various levels, in the hypoglossal nucleus, and in the cervical cord; in other parts of the cord the cells were intact. The levels at which the changes were found correspond to those in which the gray matter is most intensely diseased in the ordinary cases of amyotrophic lateral sclerosis. Moreover, it is of interest that in the muscles of the lower extremities there were found changes not unlike those in progressive amyotrophic lateral sclerosis, namely, simple atrophy of individual fibers and increase of muscle-

nuclei, yet there were no departures from normal in the ganglion-cells of the lumbar cord. Strümpell's study seems to indicate that the pyramidal tracts may degenerate in their peripheral course without being accompanied by marked change in the cell-bodies, and that changes in the peripheral motor neurones, manifesting themselves either at the peripheral end of their neuraxones or in the cell-bodies and the dendrites, may occur secondarily in point of time.

The conception of amyotrophic lateral sclerosis as a disease of the pyramidal tracts primarily, and of the gray matter, particularly of the anterior horns, secondarily, accords well with the anatomy and physiology of the neurone of to-day. As is known, the pyramidal tracts are formed by axones of the motor neurocytes in the cortex. These neuraxones degenerate after destruction of the central convolutions or after severance in any part of their course.

The changes of amyotrophic lateral sclerosis in the spinal cord, the oblongata, and in the anterior spinal roots and the muscles are distinctly recognizable by the naked eye. The cord is diminished in size, particularly the cervical portion. The dura is unchanged, except in cases of very long standing, in which it may be somewhat thickened. The pia is rarely the seat of macroscopic changes, although occasionally it is more adherent to the cord than normally. The cord is abnormally hard and unyielding, especially in the upper portions. On cross-section the gray matter shows no alteration perceptible to the naked eye, except that in some cases it is rather soft and reddish. The lateral pyramidal tracts are differentiated from the surrounding tracts by their gray color. Similar changes, though less marked, are observed in the oblongata. The normal protuberance which the well-developed hypoglossal nucleus presents on the floor of the fourth ventricle is not present. The hypoglossal nerve, and often the glossopharyngeal as well, and the anterior spinal roots, are all thin and shrunken. Furthermore, there are muscular atrophy and deformity and fixation of the joints.

Microscopic sections (Weigert's myelin stain) show that there is more or less advanced degeneration of the crossed and direct pyramidal tracts. Neuroglia stains show that the glia-tissue is but slightly increased. In some cases the anterolateral column, and especially the area intermediate between the gray matter of the anterior horns and the surface of the cord, is almost always the seat of considerable degeneration. Occasionally the lateral limiting layer may be sclerotic, and exceptionally there has been noted an involvement of the direct cerebellar tract. Next in frequency is degeneration of the posterior column, particularly of the column of Goll. This condition has been recently noted by Hektoen, Marie, Moëli, and others. The anterior commissure is sometimes involved, rarely the posterior.

The contour of the ventral horns is usually well preserved, but there is a rarefaction of the substance. The groups of cells are more or less disarranged; the neuraxones passing from them are slender and atrophic. The blood-vessels are more or less thickened; occasionally there are capillary hemorrhages, particularly of the anterior horns. The perivascular spaces are enlarged, and often the neurocytes drop out in the preparation of the specimen, leaving spaces in the ventral cornua, which gives the latter a porous appearance.

Sections stained according to Nissl's or Van Gieson's method reveal great scarcity of cells; in many sections only three or four cells are found in an

entire horn, and these are shrunken, with thin, stunted processes, or they are wholly devoid of processes. Sometimes the staining is deep and diffuse, the nucleus being absent, or the chromophilic granules are disintegrated and irregularly disseminated throughout the cell. In short, the cells are found in various stages of degeneration.

Marchi's method gives us information as to the stage of degeneration of the medullated fibers. In the oblongata, the nucleus of the hypoglossal nerve and the nucleus of Roller show changes corresponding to those

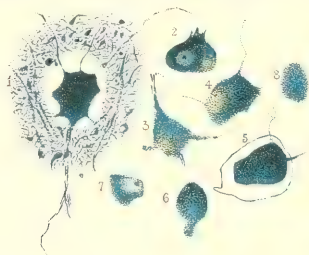


FIG. 186.—Ganglion-cells from the anterior horns of the spinal cord: 1, from lumbar region, nucleus absent, body of cell shrunken, some processes lost; 2, diseased cell, nucleus still visible; 3, dense and diffusely stained mass; 4, 5, 6, 7, 8, granular-looking cells (Hektoen).

described in the ganglion-cells of the cord. Rarely the motor nucleus of the fifth and the posterior nucleus of the vagus show degenerative changes. The changes in the pyramidal tracts at this level are, as a rule, not as intense as those in the spinal cord. Usually only a limited number of the medullated fibers are involved.

In a few cases the degeneration of the pyramidal tracts has been traced through the pons and crura cerebri to the brain. Koschewnikoff was the first to note the existence of changes in the internal capsule and white sub-

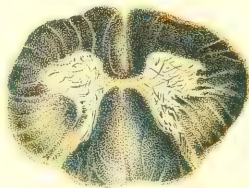


FIG. 187.—Fifth cervical segment, showing degeneration in pyramids and in Goll's column.

stance of the motor convolutions, and his observations have been corroborated by Marie, Mott, Hektoen, Sarbo, and others. The changes in the cortex of the central convolution are, in brief, a moderate degree of degeneration in the large pyramidal cells and the tangential fibers. A diminution in number of the pyramidal cells has also been noted. The deeper cellular layers of the cortex may be degenerated and the tangential fibers intact (Mott). The axones and dendrites are difficult to bring out clearly, although the cell-body and the nucleus may take the stain and appear

normal. The cells are sometimes slightly irregular in shape, and show changes in the chromophilic granules.

The lesions of the motor nerves are insignificant compared with the atrophy of the anterior roots; Kronthal recently found the motor spinal nerves intact, although the anterior-horn cells were in advanced stages of disease—a remarkable observation. While the changes in the motor nerves are slight, yet, in every case in which the nuclei of the oblongata are diseased, the bulbar nerve-trunks show corresponding degeneration. This discrepancy in involvement of nerves from different segments of the cerebro-spinal axis has not been adequately explained.

The muscles innervated by nerves from degenerated cells show simple atrophy. The remarkable feature of this atrophy is its lack of uniformity; completely degenerated fibers are found side by side with fibers perfectly preserved or with fibers in different stages of degeneration. Coincident with degeneration of the fiber, there is a progressive lipomatosis, and this is generally most marked in the tongue. The terminal muscular nerves likewise show a variable degree of sclerosis; some of them are reduced to mere fibrous-tissue bands, others are in different stages of swelling and atrophy, while still others are quite normal.

Hereditary Spinal Ataxia (Friedreich's Ataxia).—Hereditary ataxia is the name given by Friedreich and Schultze to a clinical condition dependent upon degeneration of the posterior and lateral columns of the spinal cord, associated with changes in the posterior vesicular column and the gray substance of the ventral horns. The development and size of the cord are decidedly below the normal; this deficiency of development is most striking in the cervical region, and all the constituents of the cord are involved. Microscopically there is degeneration of the posterior and lateral tracts of the cord, especially complete in Goll's column, and often quite as complete in the pyramidal tracts and in Clarke's column, while a considerable portion of Burdach's column and the direct pyramidal tract is spared. Gowers's column is almost always involved to some extent. Dejerine and Letulle believe that the disease consists in a primary proliferation of the glia in the posterior columns.

The histologic changes are, principally, an increase of neuroglia, a comparatively insignificant increase of connective tissue, and a concomitant and subsequent disappearance of the nerve-fibers. In many cases there is atrophy of the posterior roots and of the peripheral nerves, but these are by no means constant phenomena. The pia is frequently much thickened, and it is this thickening that causes the marginal sclerosis sometimes found enveloping almost the entire circumference of the cord. In such instances Friedreich's disease must be looked upon as a mixed form of sclerosis. In addition to the systemic degeneration, Dana has recently described a striking rarefaction throughout the entire cord, both in the white and in the gray matter. This rarefaction is produced by holes, which vary in size from half a millimeter to two millimeters in diameter. The spaces are distended perivascular spaces, each one being surrounded by a thin layer of connective tissue. In the cases of Friedreich's disease in which careful investigation of the vessels has been made, no marked changes were present.

Friedreich's ataxia runs in families, and may or may not be hereditary.

Hereditary Cerebellar Ataxia.—In connection with this disease, it is necessary to refer briefly to a condition, first described by Nonne, usually

known as *hereditary cerebellar ataxia*, in which the cerebellum is found to be the seat of a striking hypoplasia. In Nonne's case the hypoplasia was not limited to the cerebellum, though most marked here; but the entire central nervous system was very much reduced in size. There has not been found any involvement of the lateral or posterior tracts; in fact, the only change in the spinal cord so far described is an abnormal thinness of the anterior and posterior nerve-roots. In this connection we must refer also to a case described by Menzel, that seemingly represents a transition between these two conditions. In Menzel's case there was not only an abnormal smallness of the spinal cord, oblongata, and cerebellum, but a degeneration of the posterior and lateral columns of the cord, similar to the degeneration in Friedreich's disease, except that in Menzel's case the degeneration was most marked in the column of Burdach.

The view of Senator, that the anatomic substratum of Friedreich's ataxia is a developmental defect or atrophy of the cerebellum, has been denied by most writers. It seems to have been proved that a hyperplasia of the glia-fibers is one of the most constant changes of Friedreich's disease, but it is not of such degree that it merits the name of gliosis. In the cases in which there is a marked periependymal proliferation, this is to be looked upon as a coincidence and not as a necessary part of the disease. In short, hereditary ataxia is essentially a degeneration of the posterior roots and their continuation in the posterior columns and posterior horns, associated with disease of Clarke's column and the direct pyramidal tract.

DIFFUSE DEGENERATIONS IN THE SPINAL CORD ASSOCIATED WITH CERTAIN DISEASES, DIATHESES, INTOXICATIONS, AND INFECTIONS.

Certain general diseases, such as pernicious anemia and secondary anemia, diabetes, tuberculosis, and toxic conditions, such as ergotism and pellagra, are frequently accompanied by changes in the spinal cord that are responsible for certain definite symptoms readily demonstrable after death. The constituents of the cord that suffer most are the sensory neurones of the posterior spinal ganglia and the terminal portions of the cortical motor neurones.

Of the general diseases, **pernicious anemia** is the one most frequently accompanied by spinal changes, and tuberculosis is the next; lesions of the spinal cord also occur in diabetes and cancer. Finally, most of the exogenous and endogenous poisons may cause more or less pathologic change in the cord.

The lesions of the spinal cord which Putnam, Dana, Lichtheim, Minnich, Nonne, Bastianelli, Bowman, Burr, Russell, and many others have shown to accompany pernicious anemia are of the nature of degenerations, particularly of the posterior and lateral columns, the anterolateral and crossed pyramidal tracts, constituting a so-called combined sclerosis. Clinically the lesions cause subacute ataxic paralysis.

The lesions of the posterior columns are very similar to those occurring in tabes, except that there is no shrinkage of the columns and there is very distinct granule formation. The degeneration of the lateral columns, and sometimes also of the anterior columns, is neither so extensive nor so

regularly distributed as that of the posterior columns. In the beginning the disease is systemic, the cervicodorsal cord being most affected. After it has existed for a time the lesion is apt to show itself in the shape of irregular spots or circumscribed areas, particularly along the septa of the cord. These focal areas may, however, be of considerable extent, or they

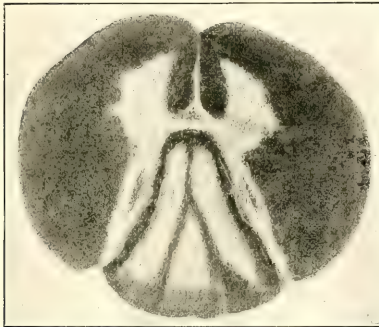


FIG. 188.—Section of spinal cord, cervical swelling, from a case of pernicious anemia (Burr).

may unite with others to form a large patch of sclerosis. Sometimes they occur on the periphery to form a peripheral zone of degeneration, associated or not with disease of the pia. In some instances the distribution of the sclerosis is so irregular that one is reminded of the lesions of disseminated

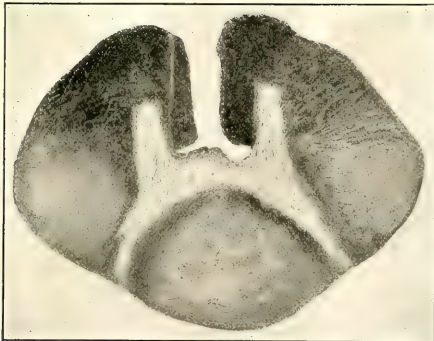


FIG. 189.—Section of spinal cord, upper dorsal region, from a case of pernicious anemia (Burr).

sclerosis; but the distinguishing feature of the latter, the preservation of the axis-cylinders, is absent. The changes in the posterior column are those usually found in ascending degenerations in the upper dorsal and cervical regions. The affection of the postero-internal columns is much more evident and advanced than that of the postero-external; in fact, the latter

show a variable degree of change, and it is to be remarked that the ventral aspect of this column, the posterior nerve-roots, and Lissauer's column are unaffected. The cord itself is considerably reduced in size. The pia is not usually implicated unless the disease is of long standing, when it may be thickened. The motor and sensory nerve-roots and the peripheral rarely show any changes.

The histologic structure of the degenerated columns is variable; in areas in which the degeneration is advanced, there are but few healthy fibers, almost all of them showing swelling of the medullary-sheath spaces, indicating the previous existence of axis-cylinders which have dropped out, distinct enlargement of the lymph-spaces, vacuolar degeneration, and, where the process is extremely marked, a considerable increase of connective tissue. If the cord be examined in the early stages of the anemia, the proportion of moderately well-preserved axis-cylinders is considerable, the principal departure from normal to be observed being a swelling of the medullary sheaths, which prevents them from taking up medullary-sheath stains. This gives them a very light coloration with Weigert's hematoxylin-stain and its modifications. When the changes are limited to this extent, there is no increase of connective tissue. The blood-vessels in advanced cases are very much diseased; there is proliferation of nuclei in the sheaths of the smaller arterioles, and the walls of the small vessels are thickened, and their lumen diminished, even up to the point of complete obstruction. Often, however, the blood-vessels present a normal appearance, and such changes as those mentioned do not occur until after there is marked connective-tissue increase in the sclerosed area. Proof of this is abundantly furnished by the examination of recent patches of degeneration in which no changes in the blood-vessels can be made out, although the cells of Clarke's column have been found atrophic and the fiber network of the ventral horns rarefied. In advanced cases there may be found considerable peri-ependymal glia proliferation and punctate hemorrhages of the gray matter. The gray matter is generally intact.

What the pathogenesis of the disease may be is unknown. Most writers who have studied this subject are inclined to believe that the depravity of the blood and the spinal lesions have a common causation, and that the latter are not dependent upon and consequential to the former. It is possible that some toxic agency produces the two conditions, just as alcohol, lead, and ergot may cause simultaneous changes in the blood and the spinal cord. It has been suggested that the immediate destruction of the medullary sheath and the degeneration of the neuraxones are dependent upon lymph-stasis due to the impoverished condition of the blood and its excess of lymph-elements. There are, however, it would seem, insuperable objections to the acceptance of this view. In the first place, the gray substance and the posterior roots are often entirely spared; secondly, there is no swelling of the glia-tissue of the cord, and no plasmatic exudate around the central canal or the blood-vessels. As a matter of fact, the symptoms that point to implication of the cord are secondary from a temporal standpoint, although they may be dependent upon the anemia.

The lesions of the spinal cord sometimes associated with **diabetes**, **tuberculosis**, and **cancer** are not unlike those just described. They confine themselves, as a rule, to the posterior columns, and consist of swelling of the nerve-fibers and axis-cylinders, shrinkage and disintegration of the

myelin, vacuolar degeneration both of the gray and the white matter, and a slight increase of neuroglia. In other cases the degenerative process in the spinal cord is irregular and diffuse, manifest both in the white substance and in the gray. The histologic structure of the lesion is that of secondary degeneration. The pathogenesis of these conditions is not unlike that given for pernicious anemia. It is extremely probable that it is some injurious agency which exercises a selective action particularly on the exogenous fibers of the spinal cord. Whether this agency is a product of metabolism, or a toxin manufactured by the original disease in a different part of the body, can only be conjectured.

Spinal-cord lesions have also been found in cases of **ergot poisoning** and **pellagra** (Italian leprosy, scurvy of the Alps), an endemic disease occurring in certain parts of Southern and Central Europe, and caused by eating corn on which a fungus has grown. The lesions have practically the same distribution as those of tabes dorsalis, and the condition is sometimes spoken of as pseudotabes. The degeneration in ergotism involves the columns of Burdach symmetrically; while the columns of Goll remain primarily free from involvement. The posterior roots show well-marked degeneration of the nerve-fibers. Hyperplasia and fibrillary metamorphosis of the parenchyma are present, without, however, any of the residua of acute inflammation. The degeneration spares the anterior root-zone, the median system of the middle zone, and Lissauer's zone. The columns of Goll may be involved in advanced cases, but the involvement is secondary. The changes accompanying pellagra are very similar to those accompanying ergot poisoning.

Marie has made some important deductions concerning the division of the degeneration accompanying tabes on the one hand, and pellagra on the other. In tabes the cornuradicular zone is diseased, while the cornucommissural zone and the posteromedian root-zone remain free; while in pellagra the cornuradicular zone is spared and the cornucommissural zone is somewhat affected, or at least much more so than in cases of tabes, and the posteromedian root-zone is degenerated. In pellagra the fiber-network and the posterior roots are intact; and therefore, as the area of the posterior root-fibers is spared, pellagra is not an exogenous disease. On the contrary, it is an endogenous disease, and has its beginning within the spinal cord. It is therefore a form of toxic myelitis.

Certain exogenous poisons (such as lead, arsenic, silver nitrate, phosphorus, strychnin, and alcohol) and toxins (such as those of tetanus, rabies, diphtheria, and septic infection) have a deleterious selective action on the spinal cord, particularly upon the cellular elements. It has been universally taught that the pernicious effects of lead are borne principally by the peripheral parts of the spinal motor neurones; but the investigations of Stieglitz, Nissl, Lugaro, Laslett, and Warrington have shown that the central parts of the neurones and the cells of the spinal ganglia are diseased as well. The cells of the anterior horns show different degrees of dislocation of the nucleus and disintegration of the chromatic particles, and even complete plasmolysis. This may be taken as an example of the reaction of the cells to the different exogenous poisons, even though some of them have apparently a selective action, such as that of arsenic for the cells of the spinal ganglia.

The toxins have likewise a selective action. The diphtheria-toxin attacks the motor cells of the anterior horns and the peripheral nerves. The streptococcus-toxin, it is believed, spares the anterior-horn cells and seems to have an affinity for the posterior roots and posterior columns, and causes disease of them which is not secondary to changes in the cells of the spinal ganglia. The changes in the cord in experimental tetanus and in those dying from the disease have been studied by many investigators, and found to be nearly identical. The changes consist of swelling of the chromatic granules, the nucleolus, and cell-body, followed by progressive chromatolysis, which may go on to disintegration of the achromatic substance, plasmolysis, and destruction of the nucleus.

All fatal cases of hydrophobia or rabies are accompanied by well-marked changes in the spinal cord and oblongata, and less constantly in the brain. These changes consist of minute hemorrhages and thrombi, and, according to Babes, of an accumulation of embryonic cells in the neighborhood of the central canal, and especially about the large cells of the motor region of the oblongata and cord. Babes considers the cell accumulations in the oblongata, the so-called "rabie tubercles," as the diagnostic lesion of hydrophobia. There is also degeneration of the motor cells and of those of the spinal ganglia.

More recently Nélis and van Gehuchten have described peculiar changes in the spinal and peripheral cerebral ganglia, particularly in the intervertebral ganglia and in the plexiform ganglia of the pneumogastric nerve. These changes consist in destruction of the large nerve-cells, brought about by the ingrowth of new cells from the capsule. These new cells invade the protoplasm of the nerve-cells and finally occupy the entire capsule. Ravenel and McCarthy consider that the capsular and cellular changes in the intervertebral ganglia, taken in connection with the clinical manifestations, afford a rapid and trustworthy means of diagnosis. Their absence, however, does not exclude rabies.

SECONDARY DEGENERATION.

By secondary degeneration is meant the destruction that takes place in tissues as the result of severance of continuity between such tissues and the parts upon which they are dependent for nutrition.

The degeneration that occurs in the spinal cord after interruption of continuity of any of its fibers, although it is similar to that which takes place in peripheral nerves after interruption of continuity, and which is known as Wallerian degeneration, differs nevertheless from the latter, inasmuch as the structures of the cord are unlike those of the peripheral nerves in many ways. The nerve-tubes of the spinal cord consist of an axis-cylinder and of a medullary sheath, but they have no definite primitive sheath corresponding to the sheath of Schwann of the peripheral nerves. They are, instead, surrounded by a covering of neuroglia which takes the place of this sheath. When a nerve is injured, a constant and striking feature in its regeneration is the proliferation of cells in the sheath of Schwann; but when the fibers of the cord are diseased, nothing of the kind follows.

Wallerian degeneration occurs in the peripheral end of a severed nerve because it is cut off from the source of its nutrition, its trophic center. The first changes are loss of translucency of the nerve-fibers, which is very

soon followed by cleavage of the myelin. Under the microscope the medullary substance is seen to be split across into masses or segments, which are separated one from another. Later, a sort of emulsification or degeneration occurs in the medullary sheath; and at this time there is a great increase in size and number of the nuclei of the sheath of Schwann. Formerly it was thought that the neuraxones underwent changes secondarily to those of the medullary sheath, but it has been proved that changes in the axones develop *pari passu* with those of the medullary sheath. The nerve-nuclei before mentioned play a very important part in nerve degeneration. In the neighborhood of the injury they swell up and undergo proliferation. After the myelin has become broken up and mixed with the degenerated remains of the axones, the débris is absorbed by the cells of the neurilemma.

Secondary degeneration of the spinal cord is classified into *ascending* and *descending degeneration*, according to the direction in which the process extends. It is usually stated that tracts or columns of the spinal cord degenerate in the same direction in which they convey impulses; for instance, that the motor tracts degenerate downward and the sensory tracts degenerate upward. We shall see presently that this is not literally true.

Secondary degeneration in the cord may be the result of a lesion in the brain, the oblongata, or in the cord itself—in short, interruption of the continuity of fibers anywhere in their course—or of the portion of the posterior root-nerves situated between the posterior spinal ganglion and the spinal cord. A brain-lesion, to produce secondary degeneration in the spinal cord, must interrupt the continuity of the motor pathway somewhere between its origin in the neurocytes of the motor area and its entrance into the oblongata. Such lesion may be the result of injury, of new growths, or of diseased blood-vessels, leading to hemorrhage or softening, or of any morbid condition that destroys the ganglion-cells of the cortex or their prolongations; it is most commonly hemorrhage or softening of the brain that gives rise to secondary degenerations in the cord.

Affections of the cord itself, that are followed by secondary degeneration, are those of complete or partial transverse section of the cord, such as occur in fracture or dislocation of the vertebræ, prolonged and continuous pressure from tuberculous spondylitis, new growths of the membranes of the cord or its bony encasement, focal inflammation, or, indeed, any condition that severs the continuity of the fibers of the cord, and thus cuts them off from their nutritive or trophic centers.

The lesions of the posterior roots that are followed by secondary degeneration are caused by inflammation or pressure affecting these roots in any part of their course between the posterior spinal ganglion and their entry into the cord. Perhaps the most common condition is inflammation either of the outer or the inner membrane.

The phenomena of secondary degeneration are best studied experimentally in lower animals, such as the monkey, and by means of the Weigert and Marchi methods of staining. Study of secondary degenerations in the spinal cord has been the most fruitful method of determining the constitution of the white columns of the cord, in delimiting their boundaries and outline, and in contributing to an interpretation of their function. If a hemisection or a total section be made of the spinal cord, the phenomena that follow are of two kinds: those that are due to the immediate destruction and

which have been considered in some detail under Acute Myelitis, and those that are the result of secondary degeneration. As the immediate result of the destruction of the spinal cord, there is formed at the level of the wound a layer of destroyed tissue or *débris* composed of blood, broken-up medullary substance, pieces of axones, and nerve-matter in various stages of transition, all bathed in lymph. In the immediate vicinity of this *débris* is an intense hyperemia and numerous small hemorrhages; between these and the adjacent normal part of the cord is an area constituted largely of leukocytes. The leukocytic infiltration extends into adjacent tissues, and concomitantly with its appearance there occurs swelling of the nerve-fibers. The myelin undergoes segmentation, and disintegrates into droplets and balls. In short, phenomena analogous to those of Wallerian degeneration, as seen in the peripheral nerves, take place. The inflammation and degeneration occur not only in one segment of the severed cord, but in both; and the extent in each segment is about equal. All the constituents of the cord partake of the retrogressive changes, but these are least marked in the ganglion-cells, which undergo chromatolysis or plasmolysis, depending upon the intensity of the destructive process. After the inflammatory phenomena subside, reparative processes begin and embryonic tissue forms. It is probable that the glia-cells do not participate to any extent in the reparative process. In addition to tissue formation from the small blood-vessels, there is proliferation of the cells of the pia, which, combined with vascular budding and proliferation, makes up connective-tissue prolongations that extend into the cord, replacing the area of destruction and uniting with the embryonic tissue that develops from within.

An examination of the area of hemisection at the middle of the first week shows the presence of a great number of large phagocytic cells, filled with particles of medullary substance. The phagocytic cells are larger than ordinary leukocytes; they contain one and sometimes two vesicular nuclei, and are to be looked upon as descendants of the fixed connective-tissue cells of the part. Numerous corpora amylacea are also found.

The most important question in regard to the repair of such destruction is, Is there a regeneration of the nerves, and particularly of the axones? The question must, at the present writing, be answered in the negative. Although it has been shown that after such lesion there are individual areas in the cicatricial formation that are penetrated by fine fibers coming apparently from the white substance above and passing to the white substance below, complete or functional regeneration never occurs. An attempt at regeneration is sometimes manifested in the appearance of new medullated fibers in the pia, just outside of the cord; it is possible that these fibers may have conducting power.

The phenomena of secondary degeneration begin immediately after the fibers have been cut off from their cells; the changes are readily appreciated as early as the third day, and are manifest throughout the entire length of the fiber. It is probable that the histologic changes pass along different nerve-fibers with varying degrees of rapidity, depending upon their size and upon their functions. Histologic changes take place earlier and are more readily apparent above the lesion in the spinal cord than below. The secondary changes are, in the beginning, swelling of the axones, which stain poorly except with acid-fuchsin. The axones continue to swell, so that the medullary sheaths are compressed, which is evident by the fact that they

stain more deeply with Weigert's hematoxylin, especially in the outer layers. If any change takes place in the neuroglia during the first week of secondary degeneration, it has not yet been determined. During the second week there occurs a complete fusion of the remains of the axones and the myelin, which leads to a complete destruction of many of the nerve-fibers. The resulting mass stains lightly with carmin, but the granules stain black with the Weigert hematoxylin. In the fourth week after secondary degeneration has begun, the axones are no longer to be made out, although the black granules are still to be seen distinctly in sections stained according to Weigert's method, and the whole area or tract in which the secondary degeneration occurs is now seen involved. This condition exists for several weeks, and it is not until about the end of the second month that the myelinic remains of the degenerated fibers begin to be absorbed. Absorption continues until the end of the fourth or fifth month, when the process is practically complete, the neural substance in the degenerated area having entirely disappeared. A consecutive increase of connective tissue begins after the second week; but, so far as experiments have been made to determine it, the glia does not undergo any proliferation until toward the end of the second month. At this time the glia-fibers begin to thicken. The neurocytes present a shrunken and beaded appearance of the protoplasmic prolongations, especially in those that pass toward the central canal and into the anterior commissure. The neuraxones are normal. Eventually the protoplasmic prolongations of the neurocytes disappear entirely, the cells having a pronounced deformed appearance. Ceni, who has recently investigated the changes in the ganglion-cells in secondary degeneration, believes that in the late stages the neuraxones of the ganglion-cells may also become diseased.

The descending degeneration that occurs in the spinal cord is confined to three columns: the anterior direct uncrossed pyramidal tract sometimes known as Türek's column, the crossed pyramidal tract, and a comma-shaped tract situated in the center of the posterolateral or Burdach's column—the head of the comma in the center, the tail reaching out toward the periphery—a column which has been studied particularly by Schultze. Naturally it depends upon the seat of the lesion and upon its extent, as to how extensive the descending degeneration will be. A lesion in the brain that severs the continuity of the motor fibers will be followed by a lesion of the crossed and direct pyramidal tracts on the opposite side of the cord, which will be so complete that it accurately delimits their outline (Fig. 190). The degeneration in the direct pyramidal tract will be traceable as far as that column extends, viz., into the lower dorsal region; while that of the crossed pyramidal tract will be traceable to the end of the cord, the extent

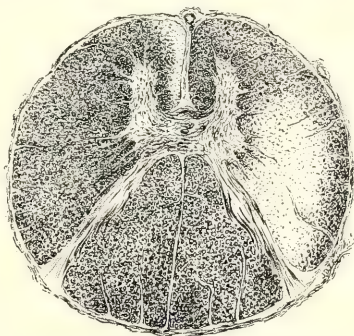


FIG. 190.—Descending degeneration after cerebral apoplexy (author's collection).

of the area growing progressively less toward the lower end of the cord.¹ If the lesion be a hemisection of the cord or a total section in the cervical region, the secondary changes in descending direction will be the same, except that the comma-shaped tract in the posterolateral column will be degenerated and traceable downward from that level. The fibers constituting this comma-shaped tract of Schultze, according to certain authorities, are made up of the descending fibers of the posterior roots; but it is more than probable that these fibers are commissural fibers, passing from one posterior horn to the opposite side, and this explains the direction of their degeneration. Schäffer, from a study of the secondary degenerations in a case of transverse lesion of the spinal cord in the lower dorsal region, produced by a gunshot wound five months previously, concludes that the descending degeneration in the posterior column can only be explained by the fact that each posterior root, after its entrance into the cord, separates into an ascending and a descending part. The descending degeneration is a result of the involvement of collaterals which stream into the anterior horns. He concludes that the descending limb is composed of fibers of medium length.

Ascending degeneration in the spinal cord is of greater sectional area than descending degeneration; and, if the lesion is severe, the degenerative area takes in a large part of the entire cord. The posterolateral region is the only one that is not degenerated far from the seat of the lesion; this is so because this region is continually augmented by the coming-in of posterior root-fibers at each successive segment. The most constant ascending degeneration occurs in the posteromedian column, which diminishes in size from below upward, and terminates in the oblongata by arborizations around the neurocytes constituting the nucleus funicularis gracilis; the direct cerebellar tract, which extends from the lower dorsal region to the cerebellum, and runs outside of the direct pyramidal tracts on the lateral borders of the cord; this tract probably has its origin in the cells of the posterior vesicular column. If the lesion is below the ninth dorsal vertebra, the area of secondary degeneration in the direct cerebellar tract is small and cannot be traced to any considerable extent. If the lesion is higher up, however, the degeneration is readily traced into the cerebellum.

Secondary ascending degeneration next occurs in the anterolateral tract, commonly known as Gowers's bundle. This tract is situated ventrally to the crossed pyramidal and the direct cerebellar tract, dorsal to the anterior root-zone; it has its origin low down in the cord, and in all probability derives its fibers from the gray substance of the anterior horn, conveying sensory impulses, which in all likelihood subserve kinesthetic functions; it has recently been traced with great accuracy, by Patrick, into the cerebellum. This column, however, it must be remarked, degenerates not only in an ascending, but also in a descending direction, although the extent of descending degeneration is very slight.

¹ The destination of the direct pyramidal tract has not yet been satisfactorily established; on account of its extent, it is supposed to go largely to the upper extremities, and most of its fibers are thought to be commissural fibers, entering into the formation of the anterior commissure. It develops its medullary sheaths, like the crossed pyramidal tract, from below upward; but it is later in the acquisition of these than the latter. In cortical lesions of the motor area there is always some degeneration in the pyramidal tracts of the same side of the cord; and this is due to a recrossing of the fibers, which occurs, according to Sherrington, about the third cervical root.

The secondary degeneration that results from lesions of the posterior roots are not so clearly understood as other forms of secondary degeneration. This subject will be considered in greater detail when speaking of locomotor ataxia. In studying secondary degenerations, it should not be forgotten that the greater number of fibers of the posterior roots in the lower part of the cord pass directly into the posterolateral column, where they remain only for a very short distance, then to pass into the gray matter of the posterior horn or into the posteromedian column, in which they run without further division or deviation up to their termination in the oblongata. The fibers that do not pass directly into the posterolateral column go at once into the posterior horn. All nerve-fibers that go from the posterior roots into the gray matter of the spinal cord, whether immediately from the roots or indirectly from the posterolateral column, form two distinct associations: one with the posterior vesicular column, the column of Clarke; the other with neurocytes of the anterior horn. The result of lesion of the posterior roots will naturally be evident in these structures.

TABES DORSALIS.

Tabes dorsalis, or locomotor ataxia, is a disease characterized by a slowly progressive degeneration of the peripheral sensory neurones. The anatomic process consists in degeneration of the posterior columns of the spinal cord.

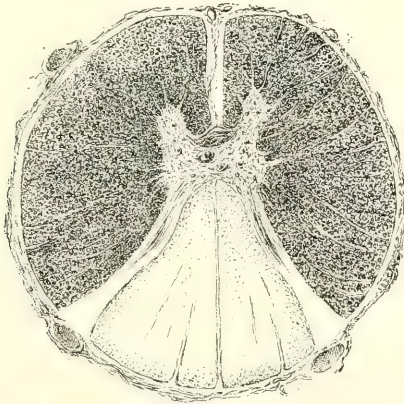


FIG 191.—Tabes dorsalis.

The lesions of tabes are not limited to the spinal cord; but, as the principal and most striking changes are found in the cord when the process is completed, it is described as a disease of that organ. The lesions of tabes dorsalis are widespread and are found in many different parts of the nervous system. The extraspinal lesions will be mentioned later.

It is probable that the primary pathologic change is in the axis-cylinders or neuraxones of the peripheral sensory neurones. According to the modern conception of the structure, arrangement, and function of neural elements,

degeneration of neuraxones does not occur without concomitant changes in the cell-bodies (the nucleus and nucleolus) of which they are prolongations. Changes in the neurocytes of the primary sensory neurones may cause degeneration or be caused by degeneration of the neuraxones, which, entering the spinal cord through the posterior roots, constitute there the intramedullary root-fibers of the posterior columns and the posterior horns.

To comprehend the occurrence and distribution of the morbid changes constituting *tabes*, an understanding of the development, architecture, and structure of the posterior horns, as they have been revealed by developmental, experimental, and histologic investigations, is necessary; and a sketch of these must be given before the nature and distribution of the lesions are discussed. The posterior columns of the spinal cord develop from the neural plates at a different period of embryonic life from the other constituents of the cord, and do not enter into the cord until a later date. The posterior columns grow into the cord from the posterior roots, which come from the spinal ganglia. They may be considered an ingrowth into the cord. A cross-section of the normal spinal cord, stained with Weigert's myelin-stain, shows the posterior columns to consist of three parts: the columns of Lissauer, of Burdach, and of Goll, enumerated from the lateral columns toward the posterior median fissure. The column of Lissauer, a narrow area situated between the lateral tracts of the cord and the column of Burdach or postero-external column, is penetrated by the posterior root, which divides it into two unequal portions, the larger portion lying ventrad to the posterior root. The inner or dorsal segment of this column is triangular in shape, and separates the horizontal fibers of the posterior roots from the vertical fibers of the postero-external column. A recognition of this zone is important, because it is the seat of striking changes early in *tabes*. The column of Burdach, composed of fibers coming from the posterior roots, in transit to the gray matter of the cord or the columns of Goll, is situated between the marginal zone of Lissauer and the postero-internal column. It is wedge-shaped, the base directed toward the periphery. The column of Goll, narrow and quadrilateral, is situated between this column and the posterior median fissure (Cajal).

At the present time, a consideration of the architecture of the posterior columns as just given is not sufficient to understand the distribution of the pathologic process in *tabes dorsalis*. The division made by Flechsig, based upon the time of the development of the myelin-sheaths, is the one that is most easily reconciled with the conception of the pathogenesis of *tabes*. It is a well-known fact that different components of a system of fibers that are apparently homologous are covered with myelin at different developmental stages. Flechsig and his disciples have utilized this fact to show that the posterior columns are composed of the following tracts, enumerated from the posterior commissure dorsally toward the periphery: An anterior root-zone (ventral zone of posterior columns), adjacent to the posterior commissure and the gray cornua; a middle root-zone which contains two kinds of fibers, referred to as fibers of the first system of the middle root-zone and fibers of the second system of the middle root-zone; a middle zone adjoining the posterior fissure, distinct from Goll's column; and a posterior zone, the dorsal portion of the posterior columns, which is divided into a lateral part, the zone of Lissauer, and a median part. These columns or zones become medullated in the following order:

First, the anterior root-zone, and shortly after this the first system of the middle root-zone, at the same time as the middle zone. Later, the column of Goll and the second system of the middle root-zone, the postero-internal root-zone, become covered with myelin-sheaths, and all at about the same time.

The posterior columns are made up of fibers of exogenous origin, which arise from the spinal ganglia; and, to a small extent, of fibers of endogenous origin, which arise from cells situated in the gray substance of the cord. Each fiber that passes into the cord from the spinal ganglia divides, after its entrance into the cord, into two branches: a long ascending branch and a short descending branch. Each of these branches gives off collaterals, which make up important constituents of the posterior columns. The root-fibers from the lower segments of the spinal cord (lumbar region) pass into the inner portions of the posterior columns and constitute the columns of Goll. The fibers of these columns terminate eventually by arborization around the nucleus of Goll's column in the oblongata. The root-fibers that enter higher up (in the dorsal and cervical regions) pass into the other parts of the posterior columns and eventually form arborizations around the nuclei in the posterior horns. The anterior root-zone of Flechsig has been shown to receive a large number of its fibers directly from the posterior roots. In addition, this zone contains a number of commissural fibers which unite the gray substance of the cord at different levels; in fact, it must be remembered that all zones contain, in variable proportion, endogenous and exogenous fibers. The fibers that go to the middle root-zone are of two kinds: those from the posterior roots, which, after passing in the posterior columns for a short distance, pass into the reticulum of Clarke's column; and those that pass from the posterior roots to make up the column of Goll, higher up. The first constitute the first system of the middle root-zone, and the second the second system of the middle root-zone. The relative composition of the middle zone of Flechsig from the posterior root-fibers has not yet been determined. The postero-external root-zone of Flechsig—or, as it is commonly called, the column of Lissauer—is made up of nerve-fibers which are much smaller and more closely packed together than any other fibers of the cord. Recent investigation of the histology of these fibers by the methods of metallic impregnation tend to show that they are formed by collaterals from the posterior roots. After continuing for some distance in the cord, they pass into the gelatinous substance, the size of the column being preserved by the continual accession of collaterals from each successive level. These constituents of the posterior columns undergo changes in tabes which are very significant. In the early stages the most striking changes of the disease are in the columns of Lissauer.

In the beginning the pathologic process confines itself to limited areas within the spinal cord, and these areas correspond to the intramedullary course of fibers that originate in the cells of the spinal ganglia or in cells from which sensory nerve-fibers arise at the periphery of the body. The widespread lesions found in old and severe cases of tabes, which will be spoken of later, are to be interpreted as manifestations of secondary degeneration.

The changes in the spinal cord vary in intensity in different cases. In some instances the dorsal cord bears the brunt of the lesion, in others the dorsolumbar region; rarely the lesion is most pronounced in the cervical

portion. In the latter case we have the so-called high or cervical tabes. Cases of tabes that come to autopsy early in the course of the disease, in which death has been the result of some intercurrent condition, show changes of much less intensity and extent than older cases.

The spinal cord may appear smaller in caliber than normal. The dura is usually normal. In some cases an increase of the cerebrospinal fluid will be found. The pia is occasionally thickened and adherent over small limited areas at certain parts of the posterior surface of the cord, but such a condition is neither typical nor constant. The degeneration in the posterior columns is often seen as a pale, white streak or band extending down the posterior surface of the cord. The posterior roots are often much

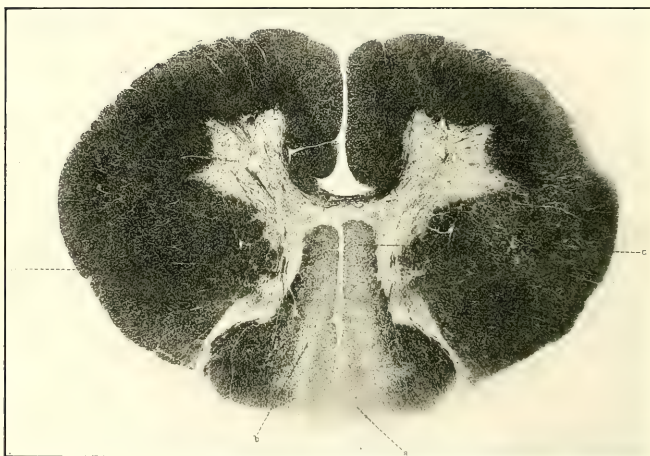


FIG. 192.—Section from the level of the third cervical segment: *a*, degeneration of the fibers coming from the sacrolumbar roots; *b*, degeneration of the fibers coming from the dorsal and lower cervical regions; *c*, septocommissural region—lightly degenerated; *d*, intact collaterals (after Babes-Marinesco).

diminished in size, and occasionally the number of strands constituting them seems to be less than normal. In other cases, however, the posterior roots appear normal to the naked eye.

When the finger is passed over the cord, a varying increase in the consistency of the posterior region is readily detected. Preservation of the cord in Müller's fluid after a short time brings out the degeneration very well, as a grayish triangle readily visible to the naked eye on cross-section of the cord. When sections of the spinal cord, stained according to the method of Weigert or some of its modifications, are examined microscopically, striking changes are at once seen in the posterior columns. A noticeable feature is the distribution of the lesion. In the cervical cord the degeneration may involve the entire posterior columns; but not infrequently it confines itself to two small strips of degeneration, which lie externally to the columns of Goll and to the columns of Lissauer. The columns of Goll

are themselves often involved, particularly the posterior border. Lower down in the cervical cord the lateral areas of degeneration in the posterior columns become more widely separated, while a new area of degeneration is frequently found between it and the column of Goll. In the dorsal cord the degenerated areas seem to increase toward the median line, while the median strip of degeneration seen above is often absent at this level. In the lumbar region the degeneration coincides accurately with the so-called external tracts (*bandelettes*), the degeneration of Lissauer's column being frequently complete. The fact that the outer part of Lissauer's column lies ventrally to the entrance of the posterior roots, and that this part is the seat of marked degeneration, has given rise to the statement that degeneration in tabes does not confine itself to the posterior column, but involves the lateral



FIG. 193.—Section from the level of the mid-dorsal region: *a*, disappearance of the collaterals of the column of Clarke; *b*, rarefaction of the collaterals of the center and of the posterior horn; *c*, middle root-zone—tabetic degeneration; *d*, ascending tabetic degeneration (after Babes-Marinesco).

column as well, thus constituting a combined sclerosis. It may be easily seen that this error has arisen because the external part of Lissauer's zone was not recognized as an integral portion of the posterior column. A striking feature in the posterior columns in many cases is the preservation of the ventral portion of the posterior column, *i e.*, the anterior root-zone of Flechsig. In many cases the postero-external root-zone remains free for a long time. This, in a general way, constitutes the distribution of the lesion. It must again be said, however, that the changes are different in the early stages of tabes from those in the late stages. In sections from advanced cases of tabes the posterior columns are completely degenerated.

In the early stages the changes are most striking in those parts of the external columns which adjoin the posterior horns, especially the middle and posterior thirds; while the changes in the column of Goll are often of slight degree.

The central canal is sometimes completely filled up, the result of proliferation of the ependyma. In advanced cases the posterior fissure may be entirely obliterated. When the sections stained by hematoxylin, carmin, and methylene-blue are examined, it will be seen that the changes are not confined to the white matter of the posterior columns, but that lesions occur in the cell-column of Clarke and in the gray matter of the posterior and anterior horns. Sections stained with methylene-blue show the cells of Clarke's columns and the posterior horns to present central or peripheral chromatolysis and excentricity of the nucleus.

Microscopically the pia may show some thickening and increase of connective tissue. In certain areas the walls of the blood-vessels are much

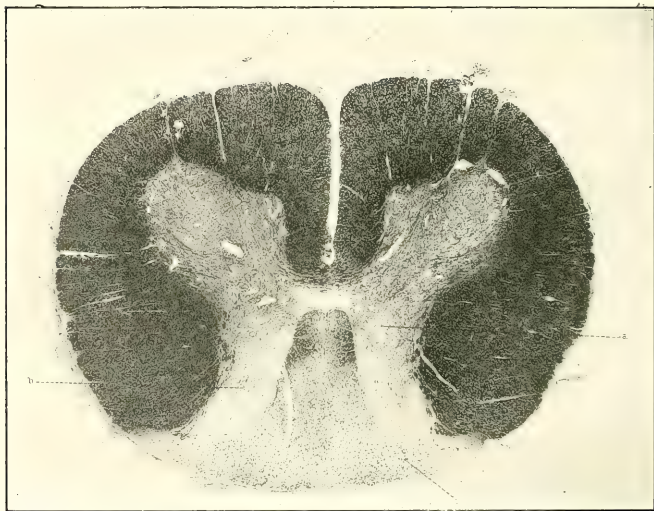


FIG. 194.—Section from the level of the lumbar swelling: *a*, atrophy of the collaterals of the central and internal gray matter; *b*, disappearance of the collaterals of the center of the posterior horn; *c*, degeneration of the median root-zone (after Babes-Marinesco).

thickened, and a fibrous zone is seen in the immediate vicinity; but in uncomplicated cases of tabes the vascular changes are never marked.

The absence, relative or complete, of nerve-fibers in the posterior columns gives them the appearance of sclerosis, even when no real increase in the sustentacular tissue is to be made out. In some cases, however, there is found genuine increase of the connective tissues, starting from the intramedullary radiations of the pia, and penetrating deeply into the substance of the posterior column. Sections stained by the Weigert or Mallory neuroglia stain reveal scattered areas of increase of the glia nuclei and fibers.

Tabes is not a disease, however, in which true sclerosis or glia proliferation constitutes an essential part of the lesion. The reticulated tissue in which the cells of Clarke's columns are embedded undergoes almost complete disappearance. Occasionally the anterior horns present a rarefied

appearance, and some of their cells have been found slightly granular.' The posterior horns are in many cases not visibly changed, while in others there is a striking disappearance of the small fibers situated in the posterior zone of the spongy substance, and of the fibers that pass in from the posterior columns.

During the past few years a number of cases of tabes have been examined with great care, in order to detect whether or not any pathologic change was to be found in the spinal ganglia. Oppenheim and Siemmerling were the first to trace the degeneration of the posterior roots into the spinal ganglia and to show the presence of degeneration of the cells of the ganglia. Raymond has described a condition which he regards as an atrophy of the spinal ganglia. He bases his opinion largely on the fact that there was an increased pigmentation of the cells. Rosin is probably right in denying that increased pigmentation is a sufficient indication of structural disease. The recent examinations made by Stroebe in three cases of tabes in various stages seem to prove the presence of degeneration, particularly in the peripheral poles of the ganglia from which the sensory nerves pass out. The cells of the ganglia were found to be shrunken, many of them abnormally thick, with deeply stained protoplasmic processes and a high degree of pigmentation, while others showed excessive vacuolation. Some of the cells were angular in contour, while others were flattened and stained deeply. In a case of advanced tabes, there seemed to be destruction and loss of all the ganglion-cells, a distention of the intercapsular space, and a proliferation of the cells of the capsules. The interstitial tissue of the spinal ganglia was increased and accompanied by nuclear proliferation. Associated with these changes in the spinal ganglia, there was an advanced degree of degeneration of the extramedullary posterior roots. The weight of evidence at the present time, based on the Nissl method, goes to show that the primary lesion of tabes is not to be found in the cells of the spinal ganglia, nor are these ganglia affected in a degree comparable to the changes found in the posterior tracts of the cord.

The changes in the peripheral nerves are variable. In some cases considerable degeneration takes place, not only in the sensory nerves, but in the motor nerves as well. The changes are found most commonly in the small nerves at the periphery of the body, it being rare to discover changes in the larger and more central trunks, such as the median or sciatic. The character of the lesion in the small nerves is that of a periaxial neuritis. When opportunity is given to examine the nervous system of patients with tabes, it is usually many years after the onset of the disease; and the changes found in the nerves of the skin may be primary, an integral part of the tabic process, or they may be secondary to the cachexia that occurs in every case of tabes. Recent investigations of the nerves of the skin, removed *intra vitam* and examined according to the osmic-acid method suggested by Heller, tend to show that the changes in the cutaneous nerves (that is, the peripheral distribution of the primary sensory neurone) are of a primary degenerative nature. Sections prepared in this way either show no nerve-fibers at all, or those that are made out are indistinctly stained and granular, and present an appearance suggestive of primary degeneration. The early changes in the retina, the peripheral filaments of the optic nerve, are quite analogous to these. The changes are not confined to the nerves of the trunk and of the extremities; they are sometimes seen in the

cranial nerves and in the sympathetic system. In fact, one of the theories of the pathogenesis of tabes holds disease of the sympathetic nerves as the most characteristic lesion. The changes in some of the cranial nerves, such as the optic, are occasionally striking; not only is the nerve-trunk itself diseased, but the intraretinal neural constituents as well.

Examination of the brain in some cases shows lesion of the cortex, particularly of the motor regions, characterized by numeric diminution of the cells and of their axones and protoplasmic processes.

The **pathogenesis of tabes** is a subject which has furnished many theories and speculations. The disease-process may begin in any part of the primary sensory neurone, from its origin in the spinal ganglion-cells, or from ganglion-cells situated at the periphery of the body, if such exist, to its arborizations around the beginning of the second sensory neurone in any part of the central nervous system, or in the ramifications between these two points. The factors that determine the point of election for the action of the toxic substances which cause the degeneration cannot be satisfactorily explained. The changes that eventually result are most marked in the intramedullary trajet of the primary sensory neurones in the posterior columns of the cord, and the distribution of the lesion conforms accurately to the distribution in systems of the fibers, the word system being used here in an embryologic and anatomic sense, and not in a physiologic. Accompanying this degeneration of the intramedullary prolongations of the posterior roots, there is a relative, and sometimes an absolute, increase of neuroglia or of the sustentacular tissue, constituting in the first instance an apparent, and in the second a real, sclerosis. The latter condition, even to a mild degree, is never seen except in ancient cases of tabes, nor does it ever assume such proportions as to warrant the assumption that the destruction of the axones is the result of it. Evidences of previous inflammation, to which the changes in the posterior columns could be attributed, do not exist. Tabes is therefore not a disease of the spinal cord, but a systemic disease of the primary sensory neurone, of exogenous origin; and the degeneration may be manifest at the periphery, in the spinal cord, and in the brain. In addition, it must be said that the tabic process does not always confine itself to the first or primary neurone. In cases of great severity and of long duration the second sensory neurone, or the nucleocortical sensory pathway, becomes involved; and likewise, but rarely, the primary motor neurone. This theory may be termed, in brief, the parenchymatous theory, the word parenchyma including the real constituents of the posterior column—the axones and dendrites of the primary sensory neurone. This theory we owe largely to Marie, whose efforts have been ably seconded by Marinesco, Goldscheider, and many other neuropathologists. Lately it has received anatomic confirmation from Wollenberg and Oppenheim.

The other theories of the pathogenesis of tabes suppose a primary increase in the interstitial tissue; that is, the connective and vascular tissues. Dejerine, for instance, believes that tabes is a systematized vascular sclerosis, which develops in the intramedullary prolongations of the posterior roots, the lesion manifesting itself primarily in the posterior roots and secondarily in the posterior columns. He believes that the changes in the blood-vessels are those of a slowly progressive and degenerative endarteritis, and that the degeneration of the posterior roots and columns is secondary.

Another theory is that to which Obersteiner and Redlich lend their

support. They believe that the spinal lesions of *tabes dorsalis* have their origin in an inflammation of the pia, which, impinging on the posterior roots at their entrance into the spinal cord, deprives them of their nutrition, and in consequence degeneration occurs. The original sclerotic pial process, to their mind, is of syphilitic origin. Nageotte has found that compression of the roots by annular pial sclerosis produces degeneration of the roots, and afterward of the columns. He believes that the vulnerable point of the posterior roots is between their entrance into the column and their origin in the spinal ganglia, and he has described in four cases typical perineuritis and mesoneuritis, which was exactly limited to the extramedullary course of the posterior spinal nerves. These theories are the principal ones that receive support from the pathologists to-day; they are by no means new. The theory of Dejerine, for instance, is but a modification and extension of that of Adamkiewicz, Buzzard, and others, who believe that primary vascular lesions are really at the bottom of the tabic lesions. It seems to the writer that the systematic distribution of the lesion in *tabes* is alone sufficient to disprove this theory. The vascular changes found in *tabes* are present in all degenerations of long standing. And, as Marie has pointed out, our present conceptions of the physiologic and anatomic unit of the nervous system does not permit the recognition of a primary sclerosis of any of the columns of the spinal cord, without changes in the cell-body from which the fibers of such columns arise.

Against the theory of posterior meningitis may be offered the objection that in the majority of cases no trace of such meningitis is to be found on microscopic examination. It is true that in many cases there is some thickening of the meninges and some adhesion to the posterior column; but it should not be forgotten that such changes may be secondary to vascular changes. Similar objections may be opposed to the theory of primary vascular degeneration. The truth is, that in the recent cases which have been carefully examined, no considerable disease of the blood-vessels has been found. Occasionally a slight thickening of the adventitia and an increase of cells are seen in some of the branches of the posterior spinal artery and in the vessels of the pia, but they are not of sufficient degree to produce the profound changes in the posterior columns. It is particularly remarkable that even in cases of great severity and of long duration there are no changes in the blood-vessels at all resembling obliterating endarteritis or the vascular alterations in transverse myelitis. In ancient cases and in the forms of syphilitic myelitis that may be accompanied by symptoms of *tabes*, changes may be found in the blood-vessels; but these changes are in reality not those of *tabes*.

PROGRESSIVE MUSCULAR ATROPHY.

Progressive muscular atrophy includes a number of distinct diseases. Formerly the term was applied to a progressive wasting of certain muscles of the body, beginning in the thenar group, later of the upper extremities, and dependent upon a gradual primary degeneration of the cells of the anterior horn in the cervical region. First described by Duchenne and Aran, this type of muscular atrophy—the progressive spinal muscular atrophy—is associated with their names. Erb was the first to separate from the group of progressive muscular atrophies of spinal origin a class of primary myopathic atrophies, the so-called *dystrophies*.

Progressive muscular atrophies were further subdivided by the separation of a type which was believed by some to depend upon primary lesion in the peripheral motor nerves of the muscles. It has been designated as progressive neurotic muscular atrophy (Hoffmann) and as progressive neural muscular atrophy (Bernhardt). Schultze has referred to it as a peculiar progressive atrophic paralysis; while Tooth, because of its localization, described it as the peroneal type of progressive muscular atrophy.

Progressive Spinal Muscular Atrophy (Type Aran-Duchenne).—Progressive spinal muscular atrophy has as its anatomic substratum an atrophy of the motor cells of the ventral horns, and degeneration of the peripheral nerves and muscles; in addition, there are somewhat less constant changes in the white columns of the spinal cord, more particularly the anterolateral ground-bundle and the pyramidal tracts. The changes may be found at any level of the cord, but are most pronounced in the cervical region. In addition to the atrophy of the cells there is a meshwork of fine fibers formed in the anterior horns, in which are seen a large number of spindle-cells. The ganglion-cells may almost entirely disappear, or they may be found in various stages of atrophy. The contour of the gray matter remains altered, which is in decided contrast to the great change of outline in anterior poliomyelitis, the chronic form of which progressive muscular atrophy much resembles, both clinically and anatomically. The anterior roots, both in their intramedullary and their extramedullary course, show degenerative changes, recognizable macroscopically by their grayish color and small size. The changes in the motor nerves can be traced to their intramuscular distribution. In the peripheral nerves completely degenerated fibers occur side by side with normal fibers and fibers in various stages of degeneration. The degenerated fibers are those coming from the ventral horns.

The wasting of the muscles is often striking. When cut across, the muscles are of a slightly reddish tint, with streaks of yellow running through them. Examined microscopically, the fibers either show simple atrophy without any marked deviation from their normal appearance, although the fibrillary segmentation is more distinct than usual, or they show a transformation of the contents of the fibers into a granular, fatty-looking material, which when absorbed leaves an empty sarcolemma studded with nuclei; this is an advanced stage of the atrophic process. In some instances the contents of the sarcolemma undergo a vitreous degeneration; this gives the muscular fiber a peculiar molten-glass appearance. When the fatty and vitreous degeneration is not well marked the increase of interstitial connective tissue and of the muscle-nuclei is marked.

As regards degeneration of the pyramidal tract, Gowers says that he has not yet met with a case of progressive muscular atrophy in which the pyramidal tracts were unaffected. When intense the degeneration can be traced up through the decussation in the oblongata, through the pons, crus, and the white substance to the cortex.

A variety of progressive spinal muscular atrophy occurring during childhood, and invariably on an hereditary basis, has been established recently by the studies of Hoffmann, Werdnig, Sachs, Thompson and Bruce, Londe, and others. Clinically it manifests itself at different periods of childhood and by the involvement of different groups of muscles. Hoffmann believes that the facts at hand point to the occurrence of at least four varieties: A form,

appearing in early childhood, in which the muscles involved are those of the hip-girdle and lower extremities—the descending spinal type; an infantile bulbar paralytic type; a Duchenne-Aran type; and transitional forms.

The morbid changes thus far found show a remarkable uniformity. They are: Symmetric and advanced degeneration of the peripheral neurones, which may implicate all from the hypoglossal downward; degeneration and disappearance of the cells of the ventral horns to such a degree that only a few cells remain in a cross-section of the cord; marked degeneration of the anterior spinal roots and of the peripheral motor nerves and their intramuscular branches, the changes in the peripheral nerves being less marked than in the spinal roots. In addition to these lesions, there have been found in every case degeneration of the pyramidal tracts, traceable in some cases as far as the decussation, but not beyond it, and most marked in the upper dorsal and cervical regions; degeneration of the anterior ground-bundle and degeneration of Türck's column.

The muscles show changes indicative of simple muscular atrophy, all stages of the process being seen in one muscle; it is rare, however, to find complete disappearance of the fibers. The nuclei are not increased, the transverse striations are moderately well preserved; in short, there is nothing to indicate that the process in the muscles is a primary one.

The **primary muscular dystrophies**, so-called primary myopathies, are divisible clinically into several types, such as the pseudohypertrophic form, the juvenile form of progressive muscular atrophy (Erb's type), and the Landouzy-Dejerine type, in which the face and shoulder-girdle are involved. The histologic changes forming the anatomic basis of the disease are hypertrophy and atrophy of the muscle-fibers, nuclear proliferation, vacuolization, segmentation of the fibers, hyperplasia of the interstitial tissue, thickening of the blood-vessels, and progressive increase of fat deposition up to a high degree of lipomatosis. The fibers always retain their transverse striation.

The question has arisen whether or not it is possible to distinguish the primary myopathies histologically. Writers described different, but in reality nonessential, alterations in the muscular fibers; to-day it is generally agreed that the histologic changes in the different clinical and etiologic forms are in reality quite similar, the various changes described corresponding to stages in the disease. Recently Sachs excised a piece of the infraspinatus muscle in a case of the Landouzy-Dejerine type, and on examination it was found that the piece included a section of the nerve, and this showed a marked degree of degeneration. This is an important finding in a disease supposed to be purely muscular.

The genesis of the dystrophies is an extremely obscure problem. Erb is of the opinion that they result from functional disturbance of the trophic centers. In other words, that functional disturbances in motor areas of the spinal cord may produce changes in the muscles, and that there is a definite relationship between the dystrophies and the spinal amyotrophies which are dependent upon distinctive changes in the spinal cord. But there is much in this disease that points to defect in the proton of the muscular fibers. The muscles may be defective from the beginning, or may be endowed with sufficient vital activity only to carry them to a certain stage of development; when this is reached, degeneration sets in. In this way may be explained the involvement of certain groups or certain associate groups of muscles;

and the changes found by Sachs in the intramuscular nerves are probably secondary.

In the peroneal type of progressive muscular atrophy the changes that have been found most constantly are those of a progressive interstitial neuritis of an extremely chronic character. Recent investigation has shown that this process is by no means confined to the peroneal nerve, for it has been traced in both anterior and posterior spinal nerves into the spinal cord. Marinesco believes that it is a simultaneous affection of the sensory and the motor nerves. Charcot and Marie, who investigated a case of this disease, found a systemic degeneration of the posterior columns simulating tabes, and atrophy of the anterior horn, which in its appearance corresponds to that of progressive muscular atrophy; and also atrophy of the nerves going to the atrophic muscles.

DISEASES OF THE OBLONGATA.

The oblongata is the upward continuation of the spinal cord, and is liable to the same diseases as the cord. There may be acute inflammation of the gray matter of the oblongata analogous to poliomyelitis, bulbomyelitis, poliomyelitis bulbi, or poliencephalitis inferior. The neurocytes of the ventral gray matter undergo progressive degeneration analogous to that of spinal progressive muscular atrophy and chronic anterior poliomyelitis, and this condition is called chronic progressive bulbar paralysis, glosso-labiolaryngeal paralysis, Duchenne's disease. The blood-vessels of the oblongata are liable to degeneration and rupture, to thrombosis and embolism, more so than the vessels of the cord; such processes constitute the anatomic basis of acute bulbar paralysis, sometimes called bulbar hemorrhage or softening. The oblongata may be the seat of cavity formation, the result of gliosis or of hemorrhage, the cavity extending from the central canal and the floor of the ventricle or from the substance of the oblongata. It may be the seat also of diffuse gliomatosis and other tumors. Secondary degeneration may extend into it from below or above. All these conditions are similar to their analogous processes of the cord, and will be briefly described.

Bulbar Paralysis.—The most common affection of the oblongata is chronic progressive bulbar paralysis, and the essential lesion of this disease is a progressive degeneration of the nuclei of the motor cranial nerves situated in the lower part of the oblongata, viz., of the hypoglossal, the pneumogastric, the accessory, the facial, and the motor nucleus fifth nerve, which is followed by atrophy and degeneration of the corresponding nerves. The roots of the hypoglossal, facial, vagus, and spinal accessory show distinct atrophy, even to the naked eye. They are thin and of a grayish-red color. The degenerative changes are most marked in the hypoglossal and the spinal accessory nuclei; less so, but still striking, in the nucleus ambiguous and the motor vagoglossopharyngeal nucleus. The inferior facial nucleus and the motor trigeminal nucleus are occasionally degenerated. In the entire hypoglossal nucleus scarcely a cell is found normal. They are either so shrunk as to be scarcely recognizable, or they have disappeared. The change in the cells is essentially the same as that of progressive spinal muscular atrophy, and are best studied in Nissl preparations.

The smaller blood-vessels are degenerated, the intima is the seat of cellular proliferation, and the perivascular lymph-spaces are distended. The

neuroglia is slightly increased around the nuclei. In some cases there has been found slight involvement of the pyramidal tracts. In exceptional instances some disease of the fillet has been made out. When the degeneration of the cells of the ventral part of the oblongata is associated with degeneration in the pyramidal tracts, we are dealing with cases of amyotrophic lateral sclerosis, and not with uncomplicated cases of bulbar paralysis. It has been proved that these cases progress more slowly to a fatal end than those in which the disease is of the pure type.

HEMORRHAGE INTO THE SPINAL CORD; HEMATOMYELIA; SPINAL APOPLEXY.

In comparison with hemorrhage of the brain, hemorrhage into the substance into the spinal cord is uncommon, and our knowledge of its pathogenesis is meager. True spinal apoplexy nearly always occurs in the cervical region. Hemorrhage into the substance of the cord may occur in any region as the result of trauma, such as a blow or a fall, even though not sufficient to cause fracture or dislocation. While the same vascular changes that give rise to cerebral hemorrhage occur in the spinal arteries, rupture rarely results because of the low and equable blood-pressure in the cord.

The gray matter is almost invariably the seat of the extravasation, and the ventral horns oftener than the dorsal. In traumatic hematomyelia the gray matter is also the usual seat of hemorrhage; but the dorsal horns, especially at the junction with the posterior commissure, are oftener affected. The reason for this is the greater vascularity of the central gray matter and the comparative looseness of the structure of the dorsal horns.

Hemorrhages into the substances of the spinal cord may be capillary or infiltrating.

Capillary hemorrhages rarely occur alone. They are usually associated with intoxications and infections, such as hydrophobia, tetanus, strychnin poisoning, etc.; they also occur in acute inflammations of the cord. Capillary hemorrhages are sometimes the principal lesion of caisson disease.

The punctate hemorrhages give to the cross-section a peculiar flecked appearance. The hemorrhages are scattered irregularly and do not follow any particular vessel. If in the white matter, the extravasations push their way between the nerve-fibers, compressing and tearing them asunder; thus, small foci of myelomalacia result.

When blood escapes from the vessels in primary or traumatic hemorrhage it takes the direction of least resistance. In traumatic hemorrhage the transverse involvement of the cord is usually marked. From the point of rupture the blood may pass for long distances upward and downward in the cord. The blood causes at first no destruction of tissue, but later it produces softening and disintegration. Van Gieson has shown that this is one method of cavity formation within the cord.

At the level of the hemorrhagic focus the destruction of tissue may be great, both in primary hematomyelia and in the traumatic forms. The secondary changes that go on in the hemorrhagic area are the same as those in cerebral apoplexy, and do not require special description.

CAVITIES OF THE SPINAL CORD.

Hydromyelia is a distention of a central canal, unattended with structural changes other than those due to compression. Its development is slow and its genesis obscure.

A cord the seat of hydromyelia, after removal from the body, is seen to be distended in segments or throughout its entire length; and when it is placed on a flat surface distinct fluctuation can be obtained. On cutting into the substance of the cord, the liquid contents of the cavity, lymph-like in character, escape. The cavity may be barely apparent to the naked eye, or it may so encroach upon the cord that only a narrow cortex remains. In shape it may be circular or irregular; and it may involve the central portion of the cord, or the greater area of it may be in a posterior horn or in the posterior columns. In very rare instances maldevelopment of the central canal is shown by the presence of a double canal, one of which may be much distended.

Microscopically the central canal is seen to be possessed of its epithelial layer, although many of the cells have degenerated. There is often slight periependymal increase of tissue. The condition of the spinal-cord components depends upon the amount of distention. Hydromyelia may predispose to glia proliferation, and thus to syringomyelia; but the two conditions are entirely distinct. In some instances microscopic examination reveals changes in the vessels of the cord; and some writers have considered the vascular changes the cause of the increase of fluid, leading to distention of the central canal. Some hold that the epithelium of the central canal has, during fetal life, a secretory function, and these cells remaining, in after-life, exercise their function and so produce an excessive amount of fluid.

Syringomyelia.—The term syringomyelia is applied to a disease characterized by the occurrence of cavities or holes within the spinal cord, surrounded by an excess of glia-tissue. Clinically the disease is variable in its symptomatology, its most striking characteristic being the association of motor, trophic, and sensory symptoms. Atrophy of certain muscles and groups of muscles, and dissociated forms of anesthesia, make up the common symptom-complex. The term syringomyelia itself carries with it no significance pointing to the nature of the morbid process on which it is dependent; it signifies merely cavity formation within the spinal cord. During the past few years, however, the term has come to have a very distinct and limited application. Cavities in the spinal cord, apart from those mentioned under hydromyelia, may result from hemorrhage, preceded or not by trauma, from inflammation (as anterior poliomyelitis), from congenital defects, from tumor formation in the cord, and from impediment to the cerebrospinal fluid; but it is not to any of these conditions that the term syringomyelia is applied in everyday usage. When the term syringomyelia is used, it conveys the idea that a cavity (usually single) exists in the spinal cord, and that this cavity has resulted from (1) a primary proliferation of glia-tissue, which, after its formation, (2) has gone on to disintegration with a resulting cavity formation—a process to which the name gliomatosis is given. It is necessary also to distinguish between cavities which are the result of simple distention of the central canal, and which are lined with epithelium, and those which are genuine new cavity formations. To the former the term hydromyelia has

been applied, on account of the fact that such cavities are usually found filled with water. The term *hydromyelia* is not used in a genetic sense, nor is its occurrence associated with definite symptomatology. It may occur in *syringomyelia*, or it may occur without the presence of the pathologic process which we mean to convey by the use of the latter term.

The formation of cavities within the spinal cord has long been recognized and described. As long ago as 1546 the condition was spoken of by Étienne; and in 1740 Morgagni and Santorini gave a very lucid description of the appearance of such cavities. It was not, however, until 1824, when Ollivier, of Angers, turned his attention to the constitution of the tissue surrounding the cavity, that any definite conception was had of such cavity formations as a disease. The name *syringomyelia* was given to it by this writer. For a long time no attempt was made to differentiate between central cavity formation occurring congenitally, distention of the central canal, and true *syringomyelia*; and it was only during the past decade that such distinction was made.



FIG. 195.—Spinal gliosis (Oppenheim).

At the present day there would seem to be at least three distinct theories regarding the occurrence or pathogenesis of *syringomyelia*, and even these do not satisfactorily explain all cases. The first, by far the most plausible and most widely accepted, is that the beginning of the disease is by the formation or occurrence of new *glia*-tissue; a proliferation of the *ependyma*-cells; and increase of the epithelium and the subepithelial cells lining the central canal; a *glia*-hyperplasia—a *gliosis*. This is followed by vascular changes, consisting of degeneration of the vessel-walls, thrombi and emboli, and punctate hemorrhages. Retrograde manifestations, leading to destruction of the new growth, and resorption of the disintegrated mass are dependent upon many factors, such as vascular changes, pressure from fluid within the central canal, termination of the natural duration of life of the *glia*-tissues, etc. To the process leading up to cavity formation the name *gliosis* is given, while to the finished product the name *syringomyelia* is given, the

symptoms of which naturally vary with the seat and extent of cavity formation.

The second view is that the disease is a manifestation of developmental defect, the original starting-point of the lesion being the embryonal remains of glia-tissue around the central canal, which should have undergone evolution or transformation, but which on account of some contingency have remained, and later on in life, under indeterminable influences, takes on a tendency to proliferation and growth, the result being not only its own destruction, but also the death of neural elements in and around it, which is followed by cavity formation. Such conditions were supposed by Virchow, who formulated the hypothesis, to follow on a congenital hydromyelia. The presence of the fluid in the central canal is thought by advocates of this view to have much to do with causing softening of the surrounding tissues, while the hemorrhages that occur with the destruction of tissue, as well as the proliferation of neuroglia, complete the process. Von Leyden, who has been the staunchest advocate of this view, believes that other parts of the cord than the central canal, such as the substantia gelatinosa and the posterior horn, may be the starting point of the lesion.

A third theory, and one that has been advocated by many French neuropathologists, is that the essential process in cavity formation is an inflammatory one, and has nothing to do with the central canal except that it occurs around it. This inflammation, occurring in the immediate environment of the central canal, and therefore called peri-ependymal myelitis, leads eventually, on account of tissue destruction combined with obstruction of the blood-vessels (thrombosis and embolism), to the formation of cavities, for which reason it is often termed *myélite cavitaire*.

A theory that has found few supporters is one that assumes vascular and lymph-stasis resulting from pressure of a tumor or other obstacles to the circulation in the posterior fossa of the skull, and from encroachment on the cord itself by tumors, by conditions that compress the cord, curvature of the spinal column, adhesion of the meninges, pachymeningitis, etc. This causes a static hydrops, which leads to distention and to the formation of one or more diverticula from the central canal.

Many objections can be urged against the acceptance of any of these contentions or hypotheses, and in truth there are individual cases which cannot be interpreted by any such conclusion. In a case reported by Gerlach the cavity formation was extensive, and in the cervical region the histologic elements were of such a nature—connective tissue, tendon-tissue, and cartilaginous tissue, muscle-elements, and capillaries—as to constitute a teratoma. Other portions of the cavity were surrounded by connective-tissue elements which could not have originated from thickening of the glia, but which suggested a mesoblastic beginning. It was believed that this tissue had its origin from the pia; although glia-tissue was abundant, there was no trace of retrogressive metamorphosis. Gerlach explains the case, as he does all others in which syringomyelic cavities have a connective-tissue border, by supposing that such cavities are congenital.

The cavities that constitute the anatomic basis of syringomyelia may be found in any part of the spinal cord, but are most frequent in the cervical region and least frequent in the lumbar region. They are found oftener in the oblongata than in the lumbar cord. They may be confined to one-half of the cord, when the process is known as unilateral gliomatosis,

or exclusively to the gray matter. The number of cavities may be one or several at the same level of the cord. In different regions of the cord there may be unconnected cavity formation; for instance, the cervical cord and the lower dorsal may each show a cavity, while the intervening portion of the cord is devoid of them. In the great majority of cases there is but one cavity, which may or may not be in communication with the central canal. This cavity usually begins in the upper part of the cervical cord, and extends into the dorsal region, but occasionally it reaches from the oblongata to the sacrum. The shape of the cavity when seen on transverse section depends largely upon, first, the length of time that it has existed, and, second, its connection or separation from the central canal. In recent cases in which the cavity develops from the central canal the shape is almost always more or less three-cornered, the base being formed by the ventral part of the central canal, and the apex indicating extension of the cavity formation into the posterior column. When the morbid process of which the cavity is a consequence is complete, the shape of the cavity is most variable. It may be circular, quadrilateral, trapeziform, spindle-form; or it may be most irregular, wide at one side of the cord and narrow at the other. On longitudinal section of the cord its shape is also variable. Nothing definite can be said about the size of the cavity, for this depends upon the amount of preceding gliomatosis and upon the destruction of the tissue. The walls of the cavity are smooth and somewhat paler in color than the surrounding cord. Rarely are they uneven with irregular pendulous shreds.

In the beginning the cavity formation shows itself in the posterior commissure, with or without communication with the central canal, and its usual direction of increase is into the posterior horn, the posterior column, and the anterior horn. The other columns of the cord and the anterior commissure are rarely the seat of cavity formation, unless the latter is so extensive that it implicates nearly the whole cord. The contents of the cavity may be a watery fluid, resembling in constitution lymph or cerebrospinal fluid, or it may be sanious. Rarely is it of hyaline appearance and jelly-like consistence.

The first departure from normal consists of a deposition or formation of cells of various shapes and irregular construction, resembling the cells lining the central canal. This cell-increase is usually in the wall of the central canal and in the subepithelial cells around it, although the central canal is not necessarily the point of departure of the proliferation. It may occur in any part of the cord, but almost invariably in the gray matter, and has a predilection for the gelatinous substance of Rolando. The central canal itself may be of normal size and appearance; or it may be distended, thus constituting genuine hydromyelia. The cell-growth proceeds from the point of original deposition toward the periphery of the cord, and in its full formation constitutes the condition known as *gliosis*. By Cornil and Ranvier it has been called neurogliar sarcoma. The tissue is made up of prolongations of glia-cells and their points of crossing, juxtaposition, and union, which had been looked upon, until Weigert showed the untenability of the view, as the body of the cell. In the immediate vicinity of such points of crossing one recognizes what is called a ground substance, a substance formed from the cells themselves, which may be homogeneous or made up of a network of transverse crossing or parallel fibers. In the vicinity in which the cell proliferation begins the cells are of larger size than toward the periphery

of the area to which the gliosis is limited, and than in the surrounding tissue through which the glia-cells are making their way. The growth of glia-cells and their proliferation cause changes in the contour and in the contents of the central canal, and destruction of surrounding tissue. In the beginning, if the process starts from the walls of the central canal, there are proliferation and shedding of the cubical epithelium lining the canal, which collects and more or less occludes the lumen. In some instances the gliosis extends into the central canal as well as around it, and in such a case the canal forms the core of an apparently lamellated mass. When the new growth is limited to one side of the canal the glia-tissue may be seen jutting into the corresponding border of the canal. On the other hand, if the glia proliferation is pronounced on opposite sides of the canal, these two surfaces may unite and thus divide the enlarged central canal into two parts, a dorsal and a ventral, or into two lateral parts, which may each afterward become individually distended to constitute true syringomyelic cavities.

In the beginning, and for an indefinite time succeeding, the formation of glia-tissue and the proliferation constitute the only departure from normal, except those changes due to the gliosis. The proliferation of cells has no relationship apparently to the course or number of blood-vessels. Microscopic examination of a section of a cord at such an early stage would show a great increase of the glia-cells around the central canal. The proliferation is particularly evident in the posterior or gray commissure. Even in this early stage the central canal may have an irregular contour, sending one or more diverticula toward the periphery. These may give the central canal on cross-section an irregular or stellate appearance.

After a time, however, very striking, but by no means typical, changes take place in the blood-vessels. The lesion of the walls of the vessel is the one that commonly results from impairment of nutrition, and consists of hyaline degeneration, particularly of the connective tissue. The intima is rarely recognizably diseased. The vessels are sometimes very much enlarged; in other instances the lumen is narrowed and often obliterated. In such cases degeneration of the vessel-walls is well advanced. Diapedesis, capillary and small arterial thrombi, extravasation, and rupture of vessels occur. Small hemorrhages are of relatively frequent occurrence, and these are manifested on microscopic examination by the presence of blood-corpuscles or of hematin crystals. The vascular lesions are most apt to occur in the center of the gliomatous tissue, a place where the morbid process is most advanced. On microscopic examination the changes in the walls of the vessels are readily recognized: the small thrombi have a dark, homogeneous appearance, while the hemorrhages have a yellowish or brownish-red tint, pointing to pigmentary remains. The staining caused by such pigment may remain long after all traces of the hemorrhage or extravasation have been removed.

These vascular derangements are speedily followed by disintegration and retrogression of the gliomatous area. As degeneration of the vessels is most advanced in the center of this mass, it is natural that terminal degeneration should be first manifest there. This is of the nature of hyaline, mucoid, or gelatinous degeneration, by which the so-called glia-cells and their fibers become transformed into a homogeneous softened mass. The disintegration of this substance and its apparent removal by transformation into a liquid give rise to the cavities, which are preceded by the formation of small holes or fissures. The latter are in the beginning separated by bundles of glia-fibers,

but soon communicate with each other to form cavities of considerable size, located centrally or otherwise. Usually the cavity is lined with a thin, delicate membrane of neuroglia-tissue with which are intermingled spheroid and oval cells. In cases that progress rapidly there may be scarcely any trace of a lining membrane.

The process of disintegration and liquid transformation takes place much more rapidly when the fluid of the central canal is in communication with the newly formed tissue. That the latter is by no means necessary for the transformation is shown by many examples in which new cavities form in the immediate environment of the central canal, but in no way communicating with it. The cavity thus formed will be of the shape of the area of gliomatosis, although its confines do not often reach as far as the preceding process did. In the middle of the mass that is undergoing destructive transformation, blood-vessels in various stages of thrombosis or obliteration are seen. If the process of softening and degeneration has extended into the central canal, the combined cavities will be readily distinguished one from another by the presence of characteristic epithelium lining the normal portion. The contents of the cavity are a serous fluid, occasionally sanious, very rarely turbid.

On examination after removal from the body, a spinal cord the seat of such a cavity or cavities may be either increased or diminished in size, the latter being more frequent. It looks flattened and thin, and the contour of the cord is destroyed. If the cavity extends throughout the entire length of the cord, the cord may be reduced to the size of an ordinary lead-pencil. If it is placed on its ventral surface and the finger carried lightly over the dorsum, the fact that its volume and consistence are diminished is easily made out. This is more apparent when the syringomyelic cavity forms a sacculated distention. On cross-section through a segment of the cord in which a cavity has formed, very distinct demarcation is seen between the gliomatous process and the surrounding tissue. The form and extent of the cavities have already been mentioned. The walls of the cavity ordinarily present the appearance of a smooth, glistening, thickened membrane, which in some instances may be stripped from its attachment, but occasionally they are irregular and pigmented. After the cord has been hardened, and stained with nuclear and medullary sheath stains, such as ammonium carmin, alum-hematoxylin, and according to the Weigert hematoxylin method, the extent of gliomatous formation and the consequent involvement of the constituents of the cord and its surroundings can be made out. No one syringomyelic cord is an exact counterpart of another, nor do sections taken from different levels in which the gliomatosis is present show the same histologic structure.

The secondary degeneration that the new growth produces in the cord depends very largely on the location and on the rapidity of development of the gliosis. The changes in the white columns are of the nature of ascending and descending degenerations. In addition to this there are, depending on the seat of the infiltration and extent of cavity formation, disappearance of cell-groups of the gray matter, destruction of the cornua, atrophy of intraspinal root-fibers, and localized areas of meningitis. Of the cell-columns, those of the anterior horns and Clarke's column are most apt to suffer. The individual cells are seen in different stages of retrograde metamorphosis, attended with granular formation and homogeneity of the

cell substance. In some instances a whole column of cells, such as Clarke's, undergoes hyaline transformation and disappearance.

The posterior columns are more frequently involved in the secondary degeneration than any other white fibers of the cord, because the gliosis and secondary cavity formation are almost always first in the posterior commissure, and this soon impinges upon the ventral field of the posterior column. The growth of glia-tissue extending into the posterior column insinuates itself between bundles of axis-cylinders and between individual nerve-fibers, thus causing an apparent rarefaction of the parenchymatous substance, and subsequently atrophy and degeneration. The direction in which the secondary degeneration extends depends upon the fibers that are destroyed, but, generally speaking, it is ascending. Extensive implication of the posterior columns will depend upon the extent of the cavity and its ramifications. One of the most remarkable forms of secondary degeneration accompanying syringomyelia is that of ascending degeneration in the direct and crossed pyramidal tracts above the focus of destruction in the cord, which is known as retrograde or cellulipetal degeneration. Such degeneration is usually on both sides of the cord, but it may be unilateral. It is a condition found only in long-standing cases.

The membranes of the cord are unaffected in the majority of cases, although a number of instances in which the pia and dura have been diseased are reported. Degeneration of the meninges, like the cavities themselves, is found most often in the cervical region, but it may occur also in the dorsal portion of the cord. The spinal ganglia have been examined in several cases, but no evidence of disease worthy of mention was found, even in instances associated during life with well-marked arthropathies.

The atrophic manifestations in the extraspinal and peripheral nerve and in the muscles are those of secondary degeneration. They do not call for specific description, except to say that the nerve-fibers occasionally show well-marked manifestations of degeneration.

The trophic changes which occur in the skin and mucous membranes, the subcutaneous cellular tissue, the joints, and the bones have nothing characteristic about them, and do not differ from those accompanying other spinal diseases which encroach upon and injure the intraspinal representation of the sympathetic nerves. One form of syringomyelia, known as Morvan's disease, after the writer who first called attention to it, and which, on account of its occurrence in a certain definite region (Brittany), is thought to be of toxic origin, has parais as its most striking clinical feature. It is barely possible that the toxic agency in cases of Morvan's disease is the bacillus of leprosy, as has been contended by Zambaco, Falcao, and others; but this seems very improbable.

The complicating or coexisting pathologic states of syringomyelia deserve a word. The most common of these are the lesions of syphilis of the central nervous system and hydrocephalus. In 130 cases of syringomyelia analyzed by Ruppberg, a state of chronic hydrocephalus was found in 15 instances. Among the more uncommon lesions are those of cervical hypertrophic meningitis, tumors at various levels of the central nervous system, including the pituitary gland and associated acromegaly, amyotrophic lateral sclerosis, and that form of combined systemic disease known as hereditary spinal ataxia.

There is very little in the etiology of syringomyelia bearing on its patho-

genesis. Trauma seems to be the most important factor in its causation, and indirectly the male sex and manual labor. It has been suggested that trauma produces hemorrhages which become encysted, and around these the gliomatous degeneration has its starting point. In a number of the cases in which trauma has been mentioned as an etiologic factor, the cases have been reported clinically only, and it is highly probable that they were cases of hematomyelopore, a condition which its discoverer (van Gieson) believes causes a distinct complex of symptoms.

Hematomyelopore.—Hematomyelopore is the name given by van Gieson to indicate a condition of the spinal cord signified by the derivation of the term, *αἷμα*, blood; *μυελός*, marrow; *πόρος*, canal—*i. e.*, a canal in the spinal cord arising from hemorrhage. The cord in the cases hitherto observed was the seat of a longitudinal column of necrosis with cavity formation. Van Gieson believes that the primary condition is a medullary hemorrhage, the blood escaping from a ruptured vessel and flowing in the direction of least resistance, namely, parallel with the columns of the cord. Cavities result from absorption of the fluid and from degeneration of the hemorrhagic exudate. They are not surrounded by a limiting membrane, but by more or less healthy nerve-tissue.

Cavity formations, which are in no way a part of any of these three conditions, may occur in the cord; but they form a part of some integral condition, such as the holes that result from disintegration of the substance of the gray matter in anterior poliomyelitis. Cavities in the cord may also be a part of some gross defect, such as spina bifida and imperfect closure of the posterior septum; or they may be compensatory, such as from a tumor in the spinal canal, or a spinal-column deformity that encroaches on the lumen of the spinal canal, causing stasis and obstruction to the flow of lymph and cerebrospinal fluid.

DISEASES OF THE MENINGES.

The coverings of the brain or meninges are the dura, the arachnoid, and the pia. The pia and arachnoid in reality constitute one membrane, and will be so considered in this article. The dura is a dense, fibrous, slightly vascular membrane, which serves the skull as periosteum and the brain as a protective covering. In it are contained the sinuses which carry the blood away from the brain and empty it into the jugular veins. On account of its connection with the skull, serving the latter as a medium of nutrition, it is liable to coincident disease or injury with the skull-bones; and, by virtue of containing the channels of exit of blood from the brain, it not infrequently becomes diseased in connection with the sinuses and with the pia. The term applied to inflammation of the dura is pachymeningitis; when the external layer of the dura is involved, it is called external pachymeningitis, and when the internal layer is diseased, internal pachymeningitis. In addition to inflammation, the dura is liable to hemorrhagic extravasations. Such extravasations may be on the dura—that is, between it and the cranial bones—in the meshes of the dura, and beneath the dura or subdural. Hemorrhages between the dura and the cranial bones are always the result of accident or destructive lesions of the bones. The extravasations are often of considerable size, separating the dura from the bone; and, as the latter is firm and resistant, the brain substance suffers serious compression. The location of the hemorrhage is rarely the same in any two instances. A blow on one side

of the head may be accompanied by epidural hemorrhage on the opposite side; a fall on the vertex may be followed by an extravasation of blood on the dura over the frontal or lateral regions of the brain. Usually the blood is in a semicoagulated state, unless the lapse of time since its occurrence is considerable. In such cases absorptive changes may have taken place. If the compression of the brain has been severe, there may be softening and laceration of its substance.

Extradural hemorrhage may occur before and after the birth of a child; especially during delivery if the labor is a difficult one. If the extravasation does not cause death within a comparatively short time, it produces, by pressure on the brain, a form of infantile cerebral palsy in the same way as similar pressure on the brain of adults produces a monoplegia or a hemiplegia. If it occurs during intra-uterine life, and particularly if it be of great extent, it may cause a variety of microgyria.

Hemorrhage into the substance of the dura is an uncommon accident; when it occurs it is usually of small size. Extravasation into the substance may, however, be associated with extradural hemorrhage due to accident, and a genuine hematoma of the dura is the result. This condition was described in many of the older English text-books as Pott's puffy tumor, from the English surgeon who originally devoted a few lines to its clinical description.

External pachymeningitis may be acute or chronic. The acute form is commonly secondary to injuries and diseases of the bone, such as osteomyelitis, the result of trauma and infection. The chronic form occurs almost exclusively in syphilis, although a chronic inflammatory condition of the external layer of the dura may be caused by trauma.

In the acute form the dura is swollen, discolored, ecchymotic, and softened. The inflammation is frequently suppurative, but because of the slight vascularity of the dura the suppuration is not usually extensive. The purulent exudate accumulates between the membrane and the skull; or it may burrow to some extent into the meshes of the membrane, and through it involve the pia and the cortex of the brain. If the inflammatory process extends into the substance of the dura, it may cause thrombosis of the sinuses.

The exudate of acute external pachymeningitis may be absorbed or it may become encysted.

External chronic pachymeningitis the result of injuries and diseases of the bone not followed by infection, and of sunstroke, consists essentially in the formation of new fibrous or scar-tissue.

External spinal pachymeningitis or *peripachymeningitis*, an inflammation of the loose cellular tissue between the dura and the spinal canal, is infrequent. When it does occur, it is almost always purulent and secondary to caries of the spine or to bedsores; it may be tuberculous. The inflammation may be limited to a single spinal segment or it may be diffuse. It is more common in the lower part of the spinal canal, for here the tissue between the dura and the bony canal is more abundant. The exudate may be purulent or fibrinous. Tuberculous granulation-tissue and caseation may be present.

Internal pachymeningitis may be acute or chronic. The acute form is usually secondary to or associated with external pachymeningitis, but may occur primarily. Internal pachymeningitis associated with certain degenerative diseases of the brain is not an uncommon condition.

Four forms are recognized: 1. A hemorrhagic form; 2. A purulent form;

3. Tuberculous pachymeningitis; 4. Syphilitic pachymeningitis. The last variety is described under Syphilitic Diseases of the Nervous System.

1. Internal Hemorrhagic Pachymeningitis.—The most common form of internal pachymeningitis is the hemorrhagic. It may be associated with the formation of a membrane. When such a membrane forms, and blood collects between it and the dura, the condition is often spoken of as hematoma of the dura. Internal hemorrhagic pachymeningitis is not infrequent in degenerative diseases of the brain, such as progressive paralysis of the insane, hereditary or Huntington's chorea, and senile dementia. It occurs sometimes with atrophy of the brain, when no inflammatory antecedent condition can be made out. Sometimes it occurs in chronic alcoholism and scorbutus. It is most frequent in adult life, but has been observed in childhood.

The seat of internal hemorrhagic pachymeningitis is most commonly over the vertical and parietal portions of the brain, in the vicinity of the falx cerebri; and then in other locations, such as the frontal and basal regions. The naked-eye appearance varies with the intensity of the process, the extent and kind of membranous formation, and with the secondary changes caused in the surrounding tissue. At a comparatively short time after the onset of the disease, there will be found on the inner surface of the dura a delicate layer of connective tissue, which leaves a number of bleeding points on endeavoring to separate it from the dura. Occasionally it does not have the appearance of a membrane, but looks as if patches of ecchymosis occurring on the inner surface of the dura had undergone a form of degeneration which gave them a reddish-brown or rust color. In a more advanced stage the membrane becomes thickened, grayish-red, tough, and vascular, adherent at some places to the internal surface of the dura, at others separated from it by a considerable quantity of blood in various stages of coagulation and disintegration. The coagulum itself often presents a striking appearance that shows that the entire amount of blood is not poured out at one time; that is, the clot will present a lamellated appearance, each successive hemorrhage being shown by the deposition of a new layer of fibrin. The quantity of blood may vary from a slight amount to as much as ten or twelve ounces.

The pathogenesis of internal hemorrhagic pachymeningitis has for a long time been the subject of debate. The principal theories enunciated for its explanation are, first, the inflammatory theory, which was taught by Virchow, and is still adhered to by most pathologists; second, the theory of primary hemorrhage and consecutive membrane formation; and third, the theory that the hemorrhage is the result of vasomotor disturbance with spasm and contraction of the blood-vessels of the brain, due to sudden diminution of intracranial pressure. The last theory is totally devoid of support. As a matter of fact, subdural hemorrhages are of two forms, those accompanying genuine inflammation of the dura, the vascular phenomena, the exudation, and the connective-tissue formation being manifest on the under surface of this membrane. In the second, noninflammatory form, the primary changes are in the dural blood-vessels, especially the capillaries, and are of the nature of fatty changes and occasionally of a hyaline character. The diseased vessels rupture, and the result is an extravasation of blood into and beneath the dura. This coagulum becomes the seat of fibrinous deposit, which later, becoming vascularized, forms a new subdural membrane.

In the inflammatory variety there are round-cell infiltration and the formation of delicate connective tissue, penetrated by immature blood-vessels, from which blood escapes either with or without rupture. The vessels are offshoots from the capillary vessels of the dura. The newly formed tissue, delicate and transparent, in which they are situated is made up of branching, fusiform cells, supported by a more or less homogeneous basement substance. The defective blood-vessels allow the transudation of blood into this tissue, and frequently they rupture with or without antecedent degenerative changes in their walls. When rupture takes place the blood does not confine itself to the meshes of the newly formed connective tissue, but accumulates between the latter and the inner surface of the dura, constituting a hematoma. Sometimes the hemorrhage is profuse; and in these cases it is usually from the veins of the dura; and the blood accumulating between the dura and pia gives rise to the condition called intermeningeal apoplexy.

The red blood-corpuscles of the extravasation undergoing degeneration leave a residue of pigmentation, which gives color to the false membrane; degenerative changes in the membrane may be attended with the deposition of calcareous material. In advanced cases, and particularly in cases in which the inflammatory process has been slow and continuous, the degeneration of the membrane is accompanied by contraction of newly formed connective tissue, giving it a tough fibrous appearance, which obliterates the blood-vessels of one part, while fresh rupture occurs in the blood-vessels of another part. In some cases limpid fluid collects between the dura and the new membrane, or between the layers of the new membrane itself; this collection of fluid has been called *hygroma*. In rare instances infection with pyogenic organisms takes place.

The changes which internal hemorrhagic pachymeningitis causes in the surrounding tissue are variable. Sometimes the exudation and membranous formation are slow, no other tissue of the brain being encroached upon; these cases are unattended with symptoms. Other cases cause marked symptoms of softening and compression, both of the pia and of the brain substance.

2. Purulent Internal Pachymeningitis.—The purulent form never occurs as a separate entity, but as a part of diffuse and extensive purulent processes in the external layer of the dura, in the dural sinuses, and occasionally in connection with advanced purulent inflammation of the pia. Histologically it resembles external purulent pachymeningitis.

3. Tuberculous Pachymeningitis.—The tuberculous form occurs only in connection with other forms of intracranial tuberculosis, especially pial tuberculosis; and even then it is an uncommon condition.

Internal hemorrhagic *spinal pachymeningitis* may occur alone, or it may be combined with cerebral pachymeningitis. It is associated with the same conditions as the latter, viz., dementia paralytica, alcoholism, and tuberculous meningitis, and it is possible that it may occur as the result of trauma. The membrane which forms on the inner surface of the dura is similar histologically to that in the cerebral variety. It is easily detached from the dura, of fibrous consistency, and shows the overgrowth of immature vessels, which easily rupture, leaving bleeding points when the membrane is lifted. Occasionally it forms adhesions with the pia, and sometimes it is associated with external pachymeningitis. The cerebrospinal fluid is usually increased

in amount, often cloudy and sometimes slightly sanious. The new membrane may be confined in extent to one or two segments of the cord, or it may extend the entire length of the cord and continue into the dura of the brain.

There is a form of chronic internal pachymeningitis, involving chiefly the cervical region, which is characterized by great thickening of the inner layer, chiefly from the deposit of a fibrous material. The condition was first described by Charcot and Joffroy, and is termed *hypertrophic cervical pachymeningitis*. (Fig. 196). The spinal cord and the nerve-roots are usually compressed. The dura may be five or ten times its normal thickness. The central canal may be dilated, and secondary degeneration of the fiber-tracts is common. The pathogenesis of the affection is obscure—syphilis plays a part; so also do injuries, exposure to cold, and overexertion. It is possible that in some cases the disease really has its starting point in the pia. Clinically the disease presents usually a characteristic picture, but at times its differentiation from syringomyelia is difficult.

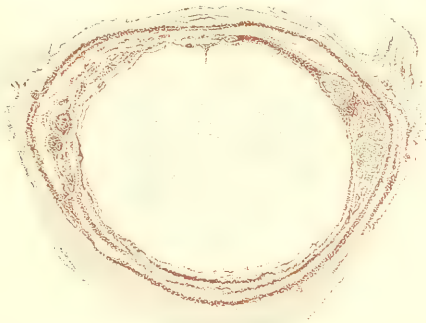


FIG. 196.—Pachymeningitis cervicalis hypertrophica: enormous thickening of dura and adhesion to pia: red points, proliferation of nuclei (Koppen).

Tumors of the Dura.—The tumors of the dura are sarcoma, osteoma, psammoma, endothelioma, and, rarely, fibroma and chondroma. Sarcoma is most common. It occurs in two forms: as a diffuse, widespread sarcomatosis of the dura, and as a circumscribed form which grows generally from the inner surface of the membrane, and consists chiefly of spindle-cells.

Osteoma of the dura mater is next in frequency; it is usually found in the falx cerebri, but occurs also in the tentorium. Often the osteoma is an exostosis of the skull, and not strictly a tumor.

Psammoma occurs exclusively or nearly so in the meninges and pineal gland. In the dura it develops from the inner surface. Psammoma is essentially sarcomatous in structure, but with deposits of calcareous concretions similar to brain-sand. The calcareous concretions are often numerous and of sufficient size to be seen by the naked eye, sometimes being as large as a small pea. Around each concretion is a formation of flattened cells which undergo hyaline degeneration. Psammoma of the dura occurs particularly at the base, and forms little white or grayish-red tumors, varying in

size up to that of the end of a finger; they are commonly symptomless, although in rare instances they produce pressure on the third and fifth nerves.

Endothelioma develops from the outer or the inner surface of the dura, and may cause greater destruction either of bone or brain than any other form of tumor.

Metastatic carcinoma occasionally occurs in the dura, usually on the inner surface extending into the brain-tissue. It may reach an enormous size and destroy the greater part of one hemisphere.

Fibroma and chondroma are usually extensions from growths in the bones of the skull.

New growths of the spinal meninges may arise from the dura or from the pia. Extradural tumors have their origin in the cellular tissue between the spinal column and the dura, or grow into the spinal canal through the intervertebral spaces. The most common variety of extradural tumor is the lipoma, but sarcoma and myxoma are also frequent. Intradural tumors arise either from the inner surface of the dura or the pia, more often from the latter. The commoner intradural tumors are myxoma, sarcoma, and fibroma. They have been found at every level of the spinal cord, the lumbar region and cauda equina being favorite locations. The pathologic changes that tumors of the spinal meninges cause in the medullary substance resemble those produced by caries of the spine. The changes are caused either by direct pressure or by obstruction to the lymph circulation and the movements of the cerebrospinal fluid. In rare instances the central canal is found distended above the seat of pressure—a condition of hydromyelia. Extradural tumors are likely to cause earlier and greater pressure upon the roots than upon the substance of the cord.

Diseases of the Pia.—The pia is a highly vascular double membrane, consisting of two layers, the inner and the outer. The inner layer, properly called the visceral pia, is in intimate contact with the brain and spinal cord. In both the brain and cord it dips into the fissures. It is the more vascular layer of the pia, and sends prolongations around the blood-vessels entering the substance of the brain, which constitute the perivascular lymph-spaces. Similar prolongations extend into the substance of the cord and furnish a support for the nutrient channels. The external or parietal layer of the pia is laid loosely on the visceral pia and bridges the convolutions of the brain, but does not dip into them. Between the visceral and the parietal pia is the pial space, which is divided into innumerable compartments of different sizes by bands of connective tissue passing from one layer of pia to the other. In the spinal canal there is no such division of the space between the parietal and the visceral pia. From the fact that the external layer of the pia is often described as a separate membrane, called the arachnoid, this space is usually termed the subarachnoid space. The interpial space forms one vast lymph-sac lined with endothelium, in which blood-vessels ramify freely, and in which pathologic products accumulate. This space, which normally is filled with cerebrospinal fluid, in diseased states may become greatly distended. The lymph-cisterns formed between the pial layers at the base of the skull are the posterior cerebellomedullary cistern, between the postero-inferior surface of the cerebellum and the oblongata, and the antero-bilateral cerebellomedullary cistern, between the antero-internal border of the cerebellum and the oblongata. These cisterns

communicate with the ventricles, the former through the foramen of Majendie, the latter through the foramina of Luschka.

The most important outlet of the interpal space is on the convexity of the brain, the communication being effected by the Pacchionian bodies, which empty the lymph into the longitudinal sinus through the parasinoidal spaces of the dura; there is no communication, however, between the pial space and subdural space. This space empties by the lymph-vessels that pass out from the base of the skull in company with the carotids, the jugulars, and other blood-vessels and nerves, into the jugular lymphatic plexus.

The lymph-spaces of the brain and spinal cord form practically one continuous area, separated by constrictions, and they may be emptied or filled the one from the other. The spinal pial space empties into the lymph-cisterns at the base of the brain, the central canal directly into the fourth ventricle. In brief, the flow of the cerebrospinal fluid is from the lateral ventricles, through the foramen of Monro into the third ventricle, through the aqueduct of Sylvius into the fourth ventricle, through the foramen of Majendie and the foramina of Luschka into the lymph-cisterns at the base, through the Pacchionian bodies to the lateral sinuses, and by way of the lymph-sheaths of the vessels and nerves passing out of the base of the skull to the jugular lymphatic plexuses. It is essential to a clear understanding of the pathologic problems in meningitis, more especially serous meningitis and acute hydrocephalus, that these anatomic facts be kept in mind. It is likewise important to remember that there is no space between the parietal pia, the so-called arachnoid pia, and the dura.

Leptomeningitis.—Leptomeningitis or inflammation of the pia mater is the most frequent and most important inflammation that occurs within the cranial cavity. It is this process that is currently meant when the term meningitis alone is used. Leptomeningitis may be divided into: 1. Serous meningitis. 2. Purulent meningitis. 3. Cellular meningitis (in which the pathologic manifestations are confined almost exclusively to the cells, and are to be made out only by microscopic examination). 4. Fibrinous meningitis.

These various forms of meningitis are in a measure dependent upon various etiologic factors, but in different cases apparently the same exciting influence may produce a serous meningitis at one time and a purulent form at another. Cerebrospinal meningitis, which occurs epidemically and sporadically, is almost invariably of a purulent nature. It is caused by one of two organisms, the epidemic form by the *Diplococcus intracellularis*, the sporadic form usually by the *Diplococcus pneumoniae*. Tuberculous meningitis, caused by the tubercle bacilli, is characterized by an eruption of tubercles and by the formation of a serous, serofibrinous, or purulent exudate. The purulent element of the exudate is the result of the pyogenic properties of the tubercle bacillus in some cases, but may be the expression of a mixed infection. Trauma, acute diseases, such as rheumatism, sunstroke, etc., seem to stand in causative relationship.

Bacteriologically, meningitis may be classified according to the bacteria causing it. There is a form of acute meningitis to which the name acute cellular meningitis is given. The recognition of cellular meningitis pathologically is of great importance, for it is the form which differs from others in frequently terminating in recovery. It is characterized by a proliferation of the fixed connective-tissue cells of the part, which accumulate in the

substance of the pia, particularly of the visceral layer. Unless the process is very well marked, it causes no change in the pia recognizable to the naked eye. If the cellular exudation is extensive the pia loses its moist, glistening appearance and becomes dry and lusterless, especially in circumscribed areas over the convexities. Sections of the pia show very distinctly the proliferation of the fixed connective-tissue cells and hyperemia. The condition is not infrequently found in the meninges of those dying from other diseases, and is often overlooked unless microscopic examination of the pia be made. Acute leptomeningitis accompanies many of the infectious diseases, such as pneumonia, typhoid fever, ulcerative endocarditis, puerperal fever, and erysipelas. It is in all likelihood due to the same factors that excite these diseases. Anything that facilitates the entrance of pyogenic bacteria into the system, and particularly into the cerebrospinal system, may be indirectly provocative of this disease. Of such conditions, trauma to the head, which acts not only by establishing a communication with the external world, but also by providing the destruction of tissue upon which bacteria may thrive, and disease of the channels and cavities adjacent to the skull-cavity, such as the middle-ear, the nasal, and accessory cavities, are by far the most important.

Serous Meningitis.—Serous meningitis displays itself in one of two forms, *external serous meningitis* (inflammatory external hydrocephalus) and *internal serous meningitis*, the inflammation occurring within the ventricles. In external serous meningitis the cortex is almost always involved to some extent, and when death occurs it is directly due to the changes in the latter. The postmortem appearance of the membranes and the intracranial contents in these cases is not a constant one; it varies with the intensity and duration of the process. In a case of sufficient severity to cause death the dura is usually found tense and injected, with moist, glistening internal surface. The parietal pia is put upon the stretch, and is glistening or cloudy. The pial space is the seat of an exudate, which is either clear, limpid, or flaky and somewhat cloudy. The exudate fills the sulci, widening them, and if at all extensive it covers the gyri, flattening them and bulging the parietal pia. Along the course of the blood-vessels, particularly the veins, the exudate is likely to show a yellowish discoloration and be of a semigelatinous consistency. When the pia is stripped from the brain, which is accomplished readily, the pial involvement is seen to be irregular, sometimes most marked over the convexities, at other times over the lateral surfaces or base. Very often slight foci of ecchymoses are scattered through the visceral pia and immediately beneath it in the substance of the cortex. On account of the intimate relationship of the meningeal blood-vessels to the cortex, pronounced changes are found in the substance of the latter in every case of this kind that is of sufficient severity to cause death. These may be so great that they constitute a meningo-encephalitis, the changes in the cortex being characterized by a serous and cellular exudation into the meshes of the gray matter, and particularly in the perivascular spaces. Coexisting with these and dependent upon them are changes in the substance of the ganglion-cells, the process being essentially one of acute degeneration, which is manifest by changes in the chromophilic bodies, as shown by the Nissl method of staining. The changes in the ventricles in typical meningitis serosa externa are slight, and may consist only of an insignificant increase in the amount of fluid. In other instances the ventricles may be distended with a clear or turbid fluid, the plexus hyperemic, and the ependyma thickened.

Occasionally external serous meningitis is sharply circumscribed, the exudation constituting what is described by some writers as localized subarachnoid effusion or subarachnoid cyst. The limitation of the exudation is probably determined by the connective-tissue bands that pass from one meningeal envelope to the other. This form of serous meningitis is almost invariably the result of direct trauma; it often causes grave but transitory symptoms, and very rarely leads to death, save in alcoholics.

Acute internal meningitis will be discussed under Hydrocephalus.

There often occurs in subjects addicted to the intemperate use of alcoholic liquors a variety of meningeal and cerebral involvement to which the name "wet brain" has been given. The designation aptly describes the macroscopic appearances of the intracranial contents. It has been contended that the vascular phenomena characteristic of inflammation do not occur in this condition. But this has not been definitely proved. As a matter of fact, there are proliferation of the cells of the meninges, exudation from the blood-vessels, and acute degeneration of the cells of the cortex. The changes in the cells are not typical of the effects of alcohol; they are the same as those that result from any other poison that manifests its injurious effects upon ganglion-cells.

Macroscopically alcoholic serous meningitis is an edematous state of the pia and brain substance occurring in alcoholic subjects who die as the result of immoderate use of alcohol, or who succumb apparently to some acute disease or after injury. In other words, it may occur with or without coexisting disease of other parts of the body. When the calvarium is removed in these cases and the dura stripped off, the pia is seen to be the seat of a variable amount of serous exudate, which occurs not only into the interpial space, but into the meshes of the meninges as well. The edema may be diffused or localized. The former is usual when it is secondary to vascular conditions, such as chronic cardiac and kidney disease, and when due to alcoholism. If the interpial fluid has existed for any considerable time, and particularly if it is of considerable quantity, it will be associated with edema and atrophy of the brain substance; in fact, in every case of alcoholic edema there are coexisting or secondary changes in the cortex. These are of great importance, and probably account for many of the psychic symptoms of chronic alcoholism. They permit a rational interpretation of those cases that die with symptoms of meningitis or meningeal irritation in which after death no adequate changes are found in the membranes to account for such termination.

Purulent Meningitis.—The commonest variety of leptomeningitis is the purulent. The pathologic product of simple purulent meningitis and that of epidemic cerebrospinal meningitis are practically similar, and we shall consider the two forms together. Neither do the lesions differ as they occur in the pia of the cord and the pia of the brain. Inflammation limited to the former is much rarer than inflammation limited to the latter; but acute leptomeningitis not infrequently extends over the entire surface of the central nervous system, and by means of the tela choroidea into the interior of the brain as well.

The exudation varies in its physical characters according to the bacterium that causes it. In the milder forms there is a good deal of serum, in which many leukocytes and a small quantity of flaky matter and fibrin are suspended. The inflammatory process is predominantly in the parietal pia, and secondarily in the visceral. The exudation of leukocytes occurs into the

perivascular spaces and along the coats of the blood-vessels, and the serous fluid distends the intermeningeal space. Very rarely is pus found upon the surface of the pia. If the leptomeningitis is a diffuse one, involving the base of the brain, the entire spinal axis may be ensheathed in a seropurulent exudate, which often extends to the end of the spinal canal. At the junction of the oblongata and the cerebellum; where the bridging of the parietal pia forms the oblongata-cerebellar cistern, the collection of seropurulent exudate and the consequent matting together of blood-vessels and nerves are greatest. The coats of the blood-vessels are infiltrated with leukocytes, and the veins are often plugged with coagula. The exudation and infiltration are not confined to the intermeningeal space and the meshes of the pia; as has been said, they sometimes occur on the free surface, but oftener they are carried by means of the tela choroidea through the substance of the brain into the ventricles, the consequence being that the choroid plexus is found swollen and covered with pus and seropurulent exudate, and the fluid of the ventricles is increased, flocculent, and turbid. In such cases the ependyma is apt to be involved.

The cortex of the brain may be edematous, with consecutive changes in its parenchyma, or it may be the seat of acute hemorrhagic encephalitis. These changes depend upon the intensity and the duration of the meningitis. The lesions of the cortex are not infrequently apparent to the naked eye, especially the swollen condition and punctate hemorrhages. Microscopic examination shows minute extravasations into the perivascular tissues, overdistention of the blood-vessels, and infiltration of the walls.

On removal of the calvarium the veins of the diploe are congested, the venous sinuses are distended, and the blood-vessels within the layers of the dura are distended. When the dura is incised and stripped back the parietal layer of the pia, although it may have lost its glistening appearance, is often transparent, and allows the congested, distended vessels of the visceral pia, and the greenish-yellow purulent and seropurulent exudate filling up the fissures and obliterating normal relationships, to shine through. The distribution and intensity of the exudate vary in different cases. In some instances the exudate is slight, and is not revealed to any great extent until after microscopic examination, when it is seen distributed along the walls of the blood-vessels and in the adjacent pial meshes.

Bacteriologic examination of the exudate and cultures made from it rarely fails to reveal the real active cause of the disease. The *Micrococcus lanceolatus* and the *Diplococcus intracellularis*, so called because the coccus is found within the body of the cell, are responsible for the acute infectious form of the disease; the former usually when the disease prevails sporadically, the latter, as a rule, for the epidemic form. It is believed that the exudate attending meningitis caused by the pneumococcus is somewhat characteristic: Of a cream-yellow color, very rarely greenish or tinged with blood, of a viscid, slightly tenacious consistence, with a tendency to smear. In epidemic cerebrospinal meningitis the character of the exudate is very similar to that already described. The distribution, however, is somewhat different. It is commonly found in the meninges of the entire central nervous system, sometimes predominating in the meninges of the cord, at other times in those of the brain, but usually most marked at the base of the brain and over the posterior surface of the cord. Lesions occur in many different viscera and parts of the body in acute cerebrospinal meningitis, and their

constancy is one of the reasons for considering this a general infectious disease, with its prominent lesion in the central nervous system. The most important of these accessory lesions are parenchymatous degeneration of the heart, liver, and kidneys, multiple abscesses in various parts of the body, purulent infiltration of synovial membranes, and diffuse adenoid hyperplasia, sometimes endocarditis. Streptococci and staphylococci may cause acute meningitis. In a few cases the colon bacillus and the typhoid bacillus have been isolated from the exudate; mixed infections may occur. It is also possible that the influenza bacillus may produce an acute leptomeningitis. In some instances the anthrax bacillus has been found as the cause of a meningitis.

Chronic Leptomeningitis.—Chronic leptomeningitis may be either a sequel of the acute form or it may be of a subacute or chronic course from its onset. In the latter it is usually associated with encephalitis. When it follows the acute form the etiologic factors mentioned for that disease are responsible; when it occurs in a subacute or chronic form its causation is not so clear. Very rarely it occurs with or is secondary to chronic internal pachymeningitis.

The location of chronic meningitis is the pia of the base or of the convexities, more frequently of the latter, in the anterior portion of the hemispheres.

The appearance of the pia in chronic meningitis varies greatly. The histologic element that predominates in the new formation is small spheeroid cells, but there is also an extensive fibrous hyperplasia, which goes on to the formation of new connective tissue. The process has a tendency to extend into the cortex, particularly along the sheaths of the blood-vessels. The new connective tissue which thus forms in the brain substance is really an outgrowth from the pial prolongations which extend through the cortex. In some instances the process is primarily degenerative, extending from the blood-vessels, and it is found associated with vascular disease in other parts of the body, such as that attending chronic alcoholism and kidney disease. On the other hand, the changes may be secondary to local pressure, such as that caused by new growths, particularly those of slow development.

The naked-eye appearances of chronic leptomeningitis are those of thickened, opaque, irregularly distributed patches of a whitish or whitish-yellow color, which are found principally in the vicinity of the larger vessels. They cause adhesion of the meninges to the cortex, and on attempting to sever them the cortical tissue is often lacerated.

It is not always possible to say whether the inflammatory process has had its origin in the meninges or in the cortex; that is, whether the process was primarily an encephalitis or a meningitis. This is particularly true of cases in which the symptoms have developed after injury, exposure to excessive heat, etc. The symptoms may have been largely mental. In cases of this kind there is adherence of the meninges to the hemisphere and to the skull-bones, and the adhesions cannot be broken up without destroying the cortex. Microscopic examination shows in the encephalon a considerable cellular infiltration, a thickening and infiltration of the blood-vessels, an obliteration of the nerve-cells and their replacement by a meshwork of indifferent tissue. The histologic changes in the meninges are those of chronic meningitis. In these cases it is more than probable that the beginning of the disease-process is in the vascular system, whose function has been perverted by trauma or other noxious agency.

Meningeal Tuberculosis.—Tuberculosis of the pia may be manifest in the shape of an isolated tubercle or by an eruption of innumerable tubercles, attended with the development of a serous, a serofibrinous, or a seropurulent exudate. When the term tuberculous meningitis is used the latter form is meant. The eruption frequently occurs in the meninges at the base of the brain. Meningeal tuberculosis occurs especially in young children, and is nearly always secondary to tuberculosis in other parts of the body.

In the removal of the brain the veins of the diploe of the skull and the sinuses are seen to be overfilled. When the brain is removed from the base of the skull and turned on the vertex the granular appearance is very striking. The white granules vary in size from that of a pin-point to that of the head of a pin. They completely stud the meninges, particularly along the line of the blood-vessels, the favorite seat being in the flexures of the pia which dip into the fissure of Sylvius and in other spaces at the base of the brain, such as around the optic chiasm, the anterior and posterior perforated spaces, and, in general, in the area included by the vessels forming the circle of Willis. In addition to these granulations or tubercles there is an exudate of a serous, serofibrinous, fibrinopurulent, or hemorrhagic nature.

In some instances the fluid exudate predominates, and the eruption of miliary tubercles is comparatively slight, while in other cases the exudate, contrasted with the amount of granulation, is insignificant. These latter forms constitute examples of so-called "dry" meningeal tuberculosis. The blood-vessels of the pia are distended, and in the pial substance there are often slight hemorrhages, particularly if the inflammation has been acute. The cortex of the brain is often edematous and swollen, especially beneath areas of extensive meningeal exudation. The convolutions, especially of the base, are flattened, while those of the convexity, if the ventricular effusions secondary to the meningitis are not very great, present a normal appearance. When the brain is laid open the ventricles are distended and contain fluid in variable quantity, often in very large amounts. The choroid plexus is tortuous and overdistended, and the ependyma often has a granular appearance.

The tubercles are made up of collections of small round cells in the perivascular sheaths of the smaller arteries, and possess the typical structure of tubercles of epithelioid and giant cells. Many are in advanced stages of caseation. The change in the blood-vessels is that of an acute endarteritis, marked by great subendothelial proliferation. Among the cells are phagocytic cells, plasma-cells, and endothelial cells.

The changes in the cortex consist principally of infiltration of cells in the superficial layer and degenerative changes in the neurocytes.

Solitary tubercle of the pia results when the tubercle bacilli take up their abode in a portion of the meninges supplied by a single branch of one of the meningeal vessels. The exudate of miliary tubercles resulting later collects to form one mass, which varies in size from that of the end of a lead-pencil to that of a hen's egg, and encroaches, according to its size, upon the substance of the brain. This form of meningeal tuberculosis is probably always secondary to a deposition of tubercle in other parts of the body, although at times no focus can be found at autopsy (Fig. 197). Unless the solitary tubercle is of more active growth than usual, and unless it encroaches upon an area of the brain possessed of specialized functions, such as one of the special sense-areas or motor areas, it is not usually suspected until

found after the death of the patient, which has been caused by some other disease.

Microscopic examination shows the isolated tubercle to have a characteristic histologic structure, and to be in various stages of caseous transformation, this process being most advanced at the center of the tissue. It is generally separated from the surrounding brain substance by an area of granulation-tissue.

Tuberculosis of the spinal pia is incomparably less frequent than of the cerebral pia. When it occurs, it is usually an extension from tuberculosis of the cerebral pia; but sometimes it develops apart from this, secondary to tuberculosis in other parts of the body—the pulmonary organs and the vertebra.

The pathogenesis and morbid anatomy of tuberculosis of the spinal pia are like those of the same disease in the pia of the brain, and do not, therefore, call for individual description. Involvement of the medullary substance is much commoner in spinal than in cerebral pial tuberculosis,

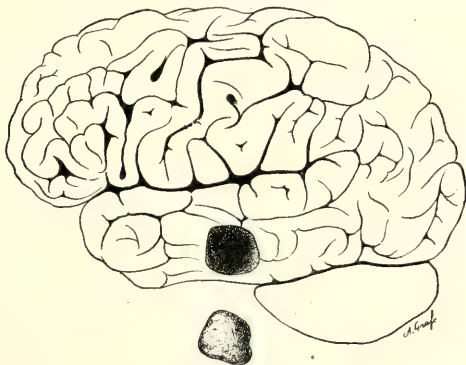


FIG. 197.—Solitary tubercle.

and most of the cases of the former are in reality tuberculous meningo-myelitis. These are referred to in the section on Myelitis.

Actinomycosis of the Central Nervous System.—See page 651.

Syphilitic Leptomeningitis.—The pia is quite susceptible to the syphilitic virus. The favorite seat of syphilitic leptomeningitis is at the base of the skull, and especially the middle fossa. Although gummatous meningitis may extend over the entire base, the interpeduncular space is the most common seat. The next most common location is the convexity, especially the frontal and the parietal lobes. In this location it may be circumscribed or diffuse, and is generally accompanied by a considerable involvement of the cortex, constituting a meningo-encephalitis. Syphilitic disease of the pia is occasionally associated with syphilitic pachymeningitis, although not necessarily so.

The pia loses its normal appearance; it is adherent to the base of the brain, the nerves, and blood-vessels, and often it can only be detached by a force that destroys these structures. It is of a grayish-white or slate

color, thickened, resistant to the touch, and often the seat of irregular nodules. The adhesions to the basal structures pervert the normal relationships of the latter. When the pia is examined microscopically, it is seen that the essential element of the lesion is granulation-tissue, consisting of round cells closely pressed together, supported by the connective-tissue stroma of the pia. The cells are collected into definite masses or they are rather evenly diffused. Newly formed vessels are present, but the walls are frequently degenerated, and retrogressive changes have occurred in the new tissue. The caseation is seen earliest in the center of the small cellular nodules. Spindle and giant cells also occur. Extensive degeneration gives to the tissue a dirty-yellow appearance; it may be pultaceous, almost fluid, and there may be serous infiltration and congestion of the blood-vessels, particularly in the depressions and sulci of the brain.

Syphilitic Disease of the Blood-vessels.—Syphilitic disease of the blood-vessels of the central nervous system is yet far from satisfactorily understood. A question that must confront everyone who sees the disastrous effects of syphilis upon the blood-vessels of the brain is, Why should these vessels, of all those in the body, be so often singled out as the seat of lesion? No satisfactory answer has yet been given. The blood-vessels particularly prone to luetic disease are those entering into the formation of the circle of Willis and the larger branches of the latter. Of the spinal arteries, none seems especially prone to disease; but it appears that the spinal veins are the seat of syphilitic perivascularitis more frequently than the cerebral veins. Recognition of syphilitic disease of the arteries of the central nervous system dates practically from the time of Heubner's work on this subject, now nearly thirty years ago. He taught that the essential lesion of syphilitic disease of the blood-vessels was an endarteritis manifesting itself particularly by destruction of the fenestrated membrane, and, on account of cellular hyperplasia, causing narrowing of the lumen or even complete occlusion. For a long time his teachings were universally accepted. They were then denied *in toto* by many, but at the present day they are recognized by all to be partially true.

Syphilis may affect the arteries, the veins, or the capillaries of the central nervous system, most frequently the arteries. There may be peri-arteritis, meso-arteritis, or endarteritis. The lesion, it matters not in which coat it shows itself, consists essentially in the production of round cells, which have their origin from the fixed connective-tissue cells of the part and the vasa vasorum. In endarteritis infiltration occurs between the fenestrated membrane and the lining of the vessel. Heubner claimed that the primary proliferation occurred in the endothelium, and he denied that any of the cells came from the vasa vasorum. After the cellular accumulation has reached a considerable extent, the new tissue is penetrated with new blood-vessels from the vasa vasorum. Eventually the newly formed tissue becomes cicatricial; dilatation of the vessel may occur, and the loss of elasticity may lead to aneurysm. In other cases the narrowing of the lumen and destruction of endothelium may lead to thrombosis which completely closes the vessel.

Gummatous peri-arteritis is characterized by yellow or yellowish-gray deposits and elevations upon the blood-vessel. It often accompanies a gummatous formation in the pia or in the substance of the brain, and microscopically the transition from the latter to the former cannot be detected.

It has the same histologic structure as other gummatous formations, although it is more apt to be found in stages of retrogression. It may be the only evidence of syphilitic disease of the blood-vessels, or it may occur associated with endarteritis.

Gummatous and degenerative changes in the blood-vessels are by no means equally distributed, and oftentimes they are not recognizable at all to the naked eye. In one artery, or in one section of an artery, there may be a typical gummatous periarteritis associated with gummatous formation elsewhere, while in another a typical endarteritis may exist. The syphilitic lesions of the vessels may in the beginning be a peri-arteritis or a periphlebitis, which is followed later by endarteritis, in consequence of defective nutrition from occlusion of the vasa vasorum.

Changes somewhat similar to these may occur in the vessels of an individual who has never had syphilis, and the two conditions which it is most difficult to distinguish from syphilitic vascular disease are tuberculosis of the vessels and angiosclerosis. The demonstration of tubercle bacilli will settle the diagnosis. Syphilitic endarteritis is distinguished from simple endarteritis particularly by the fact that in the latter fatty and calcareous changes of a most extensive kind are the rule, while in syphilis they are the exception.

Hydrocephalus.—Hydrocephalus, a pathologic increase of the cerebrospinal fluid, is of two kinds, congenital and acquired. In internal hydrocephalus the ventricles are distended; in external or intrameningeal hydrocephalus the fluid is in the interpal spaces. The most common cause of acute hydrocephalus is inflammation of the pia; in internal hydrocephalus a serous inflammation of the pia lining the ventricles, or internal serous meningitis, usually secondary to inflammation of the pia of the convexities. It has been taught by many pathologists that the telæ and choroid plexus are never primarily diseased, but the occurrence of internal serous meningitis has been put upon a firm foundation by Quinke, Boenninghaus, and others. Primary inflammation of the pia of the ventricles results in distention of the latter with a serous exudate. The effusion may be so great that it compresses the brain-hemispheres against the skull. The ependyma becomes opaque and thick, especially in long-standing cases. The choroid plexus is hyperemic and the walls of the vessels infiltrated. Compression of the tela against the tentorium causes compression of the veins of Galen and consequent stasis of the blood and lymph stream, the distention of the ventricles closing the third and fourth ventricles.

It is probable that the majority of cases of congenital hydrocephalus in which no other lesion of the brain than the distention of ventricles and flattening and atrophy of the convolutions and disarrangement of the relationships of the constituents of the brain can be found are due to endymitis.



FIG. 198.—Syphilitic disease of a cerebral vessel (author's collection).

And although the time at which the original process occurred in the ependyma is so remote that nothing is known of the causation of the inflammation, the fact remains that disease of the ependyma may give rise to similar hydrocephalus at other periods of life.

Congenital hydrocephalus may be secondary to defective development or malformation of the encephalon; to all diseases and new growths of these structures that may occur during intra-uterine life; and to any condition causing retardation of the formative process which closes in the cerebral vesicles and results in rotation of the brain.

The causes of acquired hydrocephalus of a primary nature are not more definitely determined than those of the congenital. The secondary forms of acquired hydrocephalus develop from disturbance of the relationship between blood-pressure and lymph-pressure. It is found in inflammatory conditions of the brain and its coverings, in brain-tumors, particularly those developing in the posterior fossa of the skull and in those encroaching upon the cavities of the ventricles or some of its avenues of communication. Internal hydrocephalus of the adult, apart from acute meningitis, is almost always due to a subtentorial tumor, which causes the accumulation of fluid either by compressing the veins of Galen, by compressing the outlet from the lateral ventricles, or by compressing both of these.

Hydrocephalus produces a variable enlargement of the head, at times up to a circumference of one hundred centimeters. The head is typically dolichocephalic. In some cases of congenital hydrocephalus there is no enlargement of the head, a condition that is probably due to early ossification of the sutures. When the skull-cap is removed the membranes are seen to be on the stretch up to the point of rupture. The dura is often extremely adherent to the skull, and the two coats of the pia are very thin. The convolutions and the fissures are obliterated. The tissue separating the pia from the distended ventricles may be as thin as a sheet of paper. When the process is not far advanced, it may be possible to distinguish the primary sulci and the principal convolutions, but differentiation between the white and gray matter is early lost. Occasionally one hemisphere is more atrophic and the ventricular space correspondingly larger than the other. The amount of fluid in the ventricles varies from a few ounces up to 15 quarts. The ventricular system, including the four ventricles and their avenues of communication, may all be distended and converted into one pouch-like sacculated cavity, the narrow channels and aqueducts being almost completely effaced. Along the interior of the ventricles the vascular prolongations of the choroid plexus are seen long drawn out and delicate. Sometimes the fourth ventricle is alone distended, the distention causing much pressure-atrophy of the oblongata and cerebellum.

The changes that hydrocephalus may effect in the relation between the constituent parts of the encephalon, particularly the brain, the cerebellum, and the oblongata, are often great. When the ependyma of the ventricle and the choroid plexuses are examined carefully, there will be found a certain amount of granulation-tissue which is considered to be of inflammatory origin. Examination of the cortex and the tissue forming the wall shows atrophic changes of varying degrees.

Thrombosis of the Dural Sinuses.—The venous sinuses of the dura are wide channels between the two walls of the dura that receive the blood from the brain and pour it into the jugular veins. They are often the

seat of disease, especially when the cranial bones are injured, and in meningitis. The pathologic lesions in the sinuses are essentially the same as those that occur in veins: Thrombosis with or without inflammation. The infective form of thrombosis is the result of contiguous inflammation extending to the dura. The most frequent cause is a purulent disease of the middle ear, with osteomyelitis of the petrous portion of the temporal bone; the sinus most liable to infection is the lateral.

The essential cause of sinus-thrombosis not dependent on suppurative sinus-phlebitis is a condition of marasmus, produced by exhausting and infectious diseases, particularly in the very young and in the senile. The longitudinal sinus is most frequently the seat of this form of thrombosis. The thrombus itself has the characteristics of other marasmic thrombi; it is firm, does not crumble easily, is somewhat irregular in extent, of a yellowish or yellowish-red color; it is often stratified, showing that the coagulation has occurred at different times. Such thrombi are occasionally associated with rupture of some of the meningeal vessels. Similar conditions also occur in profound anemia, especially chlorosis.

In the infective thrombosis of the venous sinuses the thrombus is a dark, pasty, reddish, disintegrating mass. It is commonly found associated with some degree of purulent leptomeningitis and encephalitis. Fragments of this mass becoming detached and passing into the venous circulation may lodge in different parts of the body, especially the lungs, and constitute metastatic abscesses. When the infective process is not of sufficient severity to cause destruction or disintegration of the walls of the sinus, the clot which forms may become organized by the development in it of vascular connective tissue from the adjacent dura.

In the marasmic form the clot may undergo organization or it may become absorbed. This form may, however, produce extensive softening of the brain by an extension into the cerebral veins, and superficial encephalomalacia may result.

DISEASES OF THE BRAIN.

Malformations of the Brain.—Malformations of the brain vary in point of severity from so slight a degree that they can only be detected when compared with a normal brain, up to complete absence of the brain. The word malformation of the brain is used here in its pathologic sense to be synonymous with perverted development. Degrees and seats of arrested development are most readily understood when it is borne in mind that the intracranial contents develop from three vesicles or three vesicular enlargements of the medullary tube; and as the vesicle from which develops the forebrain is the part that has greatest growth and expansion, it naturally follows that it is the part to represent most striking defects of development. The next most common seat of malformation is that portion of the encephalon that develops from the posterior vesicle, and then most infrequently those developing from the interbrain and midbrain vesicles.

Malformations of the brain may be classified according to the completeness with which the defect goes on, and causes an arrest of all or only a part of the structures developing from a cerebral blood-vessel, and according to an increase of development which may occur in the parts arising from a cerebral blood-vessel. In this way the states of malformation might be considered under the heads of—

1. **Hyperplasia**, signifying an increase of the constituents of the cerebral vesicle and the tissues that develop from it.

2. **Hypoplasia**, the opposite of the above condition.

3. **Heteroplasia**, a condition in which the formation from a cerebral vesicle becomes displaced or transplanted from its normal seat.

Hyperplasia of the brain constitutes a condition that may be called true hypertrophy, and is an extremely rare condition. Embryologically and histologically it depends upon an excessive epiblastic development of neuroglia-tissue, the white substance of the brain being increased disproportionately to the gray, and commensurate with the increase of neuroglia there is a diminution of the nervous parenchyma. Hyperplasia of the brain substance is almost uniformly a congenital condition, although it may develop after birth. Many pathologists, however, look upon the latter condition as a gliomatosis, and reserve the designation hyperplasia to those cases in which the beginning dates from the development of the blastodermic membrane. In these cases the osseous formation of the skull is hindered in proportion to the degree of hyperplasia, and thus it may vary from pronounced separation of the sutures and fontanels up to scattered deposition of bone in membranous formations. In the less-marked forms the membranes of the brain are encroached upon and adherent to the cortex, and the cavities of the brain and the brain-ganglia are in a like way encroached upon and compressed by the extension of the tissue inward. In extreme cases of development the epicranial and cranial structures may be practically obliterated.

Hypoplasia of the encephalon is not an uncommon condition. It always bespeaks a congenital defect, and practically it includes all forms of arrested development. It does not, however, include those cases in which there has been no development of brain substance after the formation of the cerebral vesicles, and to which the name agensis has been given. The latter condition must be considered by itself. It is a very rare occurrence, or at least it may be said that a complete absence of any developmental process in the cerebral vesicles is scarcely ever seen. Partial agensis, whether it be of a hemisphere, a constituent of the interbrain or midbrain, or of a part of a hemisphere, including defective fissural and convolution formation, is not an uncommon condition. To these gradations of hypoplasia different names to designate the limitations and degrees of malformation have been given. Thus, anencephalia signifies absence of the cerebrum; micrencephalia signifies an atrophic condition of the entire brain; agyria, an agensis of gyri or convolutions; and microgyria, an undeveloped state of gyri or convolutions. In addition to these there may be described a condition in which there is absence or rudimentary development of certain connecting parts of the brain, such as the callosum and the fornix.

The actual causations of the malformations of the encephalon due to defective development are largely conjectural, the conjectures being based, however, on sound reasoning from embryologic data. So far as experimental work has been done on the ova of the lower animals, such as chicks, the results are in accord with our beliefs. The beginning of the malformation may date from the time of formation of the primary constituents of the epiblastic and mesoblastic structures. There may from that time exist a disturbance of the environmental relationship of the proton going to form the cerebral vesicles, which is manifest in a more advanced degree of development by a hindrance in the formation of the structures for the develop-

ment of which it is intended. The causative factors of such disturbance of reciprocal relationship cannot be stated positively. There would seem to be little doubt, however, that they may date back as far as the segmentation of the ovule, or they may occur at any time during intra-uterine life. It is probable that the period of greatest danger to normal development is during the early months of the embryo, and that the immediate danger is a diseased state of the amnion, which causes or allows adhesions to form between it and the cephalic end of the embryo. If the adhesion is complete and occurs early, the result may be total agenesia. If it occurs somewhat later, the maldevelopment may be manifest by anencephalia. If later yet and only partial, the degree of hypoplasia will be very variable. It is unnecessary to enumerate here the conditions that may give rise to such amniotic disease, but in addition to the manifestations of inherited disease those due to psychic and somatic injury may be mentioned.

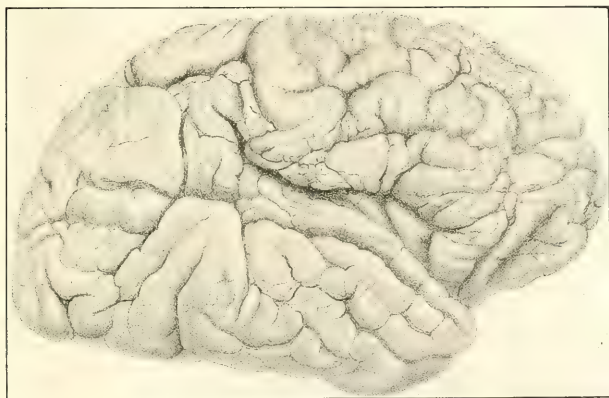


FIG. 199.—Microgyria (Otto).

In addition to these, the most important causes of partial anencephalia is intra-uterine ependymitis, accompanied by enormous liquid exudate which offers physical resistance to the development of brain-tissue. Arrest of development may also be due to disease of the brain itself during the intra-uterine life of the child. Such diseases are encephalitis, rupture and thrombosis of blood-vessels, and other conditions leading to a degree of hydrocephalus the origin of which we do not know.

Cases of anencephalia of an advanced degree, so-called total anencephalia, are always associated with a lack of development of the coverings of the brain, soft and hard. In place of the brain there is found a vascular, membranous structure of embryologic mesoblastic formation. This condition is rarely found except occasionally in children born before full term. In partial anencephalia there may be almost complete absence of the hemisphere, or partial absence; but it matters not how complete the process of defective development leading up to it has been, some rudimentary remains of the hemispheres will always be found. In some cases it is so advanced that

only the callosum in a rudimentary state remains. The hypoplasia may be uniform in the distribution, the lack of development being as manifest in one pole of the brain as in the other, and such conditions are uniformly accompanied by microcephalia. This condition of the brain and its bony covering is naturally associated with microgyria—undeveloped fissural formation. The principal fissures are usually normally laid down and well marked; but the secondary sulci and the resulting convolution of the brain are defective up to the point of nearly complete absence. Cases of micrencephalia are usually associated with imperfect development of other constituents of the cerebrospinal axis, and it is not uncommon to find an undeveloped condition of the cerebellum, defective medullation of certain tracts in the pons, oblongata, and cord, particularly those that take on such incasement late in intra-uterine life, such as the pyramidal tracts and the columns of Goll.

Histologic examination of the cortex and of the tracts of such brains reveals striking and instructive changes. Such investigations have been made by Hammarberg.

Partial hypoplasia is a much more common condition than that just described. It is usually of one cerebral or cerebellar hemisphere, and has a special predilection for one of the poles of the former. Partial hypoplasia is associated with imperfect development of the convolutions, just as micrencephalia is, and is often accompanied with asymmetry of the skull. When the lesion is of the cerebellum, the tracts which grow out of this segment of the nervous system into the cord and brain-axis are naturally completely deficient.

The most important and withal most common malformation of the encephalon is a partial agenesis of the cerebrum. The usual seat of such agenesis is the hemispheres. Partial agenesis constitutes the condition known as porencephalia, or porencephalus, a word signifying pore formation or cavity formation of the brain. Porencephalia was first described by Heschl, but it was due to the work of Kundrat, a quarter of a century later, that the importance of the condition as forming the anatomic basis of a number of diseases was first recognized. In porencephalia there is a lack of development of the brain-tissue, which may vary from such slight cortical defect that it is manifest merely by a depression on the surface of the hemisphere, up to one of such extent that the cavity remaining where cortical tissues should develop is so great that it communicates with the pial space on the outside and the ventricles on the inside. In addition to the cavity formation itself, there is always imperfect development in the immediate vicinity of the cavity, which is taken to indicate that the process of arrested development was complete in the center, but extended from this with a decreasing degree of intensity. The cessation of development usually causes a destruction of the relationship existing between the surrounding parts. Porencephalia is usually of the central and parietal lobes of the hemispheres, although it is found in the temporal and occipital regions. The relationships of the pia to the porencephalic cavity are important. The visceral pia dips down, covering the walls of the cavity; and if the latter is so extensive that it communicates with the ventricles, the pia may be placed there as far as the beginning of the ependyma. The parietal pia arches over the cavity. The accompanying changes in other parts of the central nervous system and in the skull depend upon the seat of the partial agenesis and on the date of

its origin. If it is of the motor regions of the brain, and if the cessation in development occurred early, there will be total absence of development in the projections, commissural and association tracts belonging to this part of the central nervous system. Such defect may therefore be manifest in the brain-axis, in the callosum, in the cerebellum, and in the spinal cord. Likewise, if the porencephalia be of the parietal, frontal, or temporal regions, analogous widespread developmental defects may be found. Not infrequently there is asymmetry of the skull, due to imperfect development of the calvaria over the hemisphere the seat of the porencephalia. Microscopic examination of the cortical tissue adjacent to the cavity shows various degrees of rudimentary development of the cortical constituents.

The causes of partial agenesis or porencephalia are in dispute. It has been contended by some that all forms of cavity-formation, it matters not what the time of their origin or the immediate exciting cause has been, should be included under the title porencephalia. According to this view, we must include the cavities that arise from secondary changes following blocking of blood-vessels or hemorrhage. Although everyone must admit the formation of cavities in the brain after this fashion, there exists no reason why the completed result of the diseases leading up to them should be divorced from the diseases themselves, and such cavities may well be designated as pseudoporencephalia, or, better still, acquired porencephalia, in contradistinction to the form just described, which is a congenital condition in every instance. The causes of partial agenesis do not differ, except in degree, from those of complete agenesis, and they are to be referred to causes interfering with the proper maturation of the ovule.

Embolism and Thrombosis of the Brain; Encephalomalacia.—The causes of embolism and thrombosis of cerebral vessels do not differ from those in other parts of the body. Embolism or thrombosis leads promptly to softening of the brain-area supplied by the occluded vessel.

The principal causes of cerebral embolism are valvular disease of the heart, particularly of the aortic and mitral valves. In some instances the embolus has its origin in a thrombus in the heart, in a venous thrombus (crossed embolism through a patulous foramen ovale), or more rarely in the arteries that supply the brain.

Thrombosis occurs in the brain in diseases of the cerebral vessels, in marantic and infectious conditions. The arteries of the left side of the brain are more frequently involved in thrombosis and embolism than those of the right, especially the Sylvian artery and its branches, the anterior capsulonuclear branch most frequently of all. This latter passes to the anterior limb of the internal capsule and to the basal ganglia. Next in frequency is the corresponding posterior branch. The cerebral arteries of the cortex are the next in frequency and in the following order: the median, the posterior, and the anterior. Thus the deeper branches are occluded oftener than the superficial, a condition that is explainable not alone by the smaller caliber of the former, but by their vertical direction. Other parts of the brain may be involved also. Foci of softening occur in the pons and the oblongata, but softening in the cerebellum is rare.

In cases in which death takes place so soon after occlusion that softening does not have time to take place, the appearances postmortem are those of anemia of the parts of the brain dependent upon the occluded vessel for nutrition, and a variable amount of venous hyperemia. When an arterial

trunk, such as the artery of the Sylvian fissure, is occluded, the softening may involve nearly the entire hemisphere; and if both Sylvian arteries are occluded, the resulting encephalomalacia may involve practically the entire brain.

Cerebral softening is divided into red, white, and yellow softening, distinguished according to their naked-eye appearances.

White softening refers to pure anemic necrosis without the admixture of blood in the detritus. Red softening means that more or less blood has been added to the dead tissue either from venous or capillary regurgitation into the anemic area or from hemorrhages in the vicinity. Yellow softening is generally a late stage in the red when changes have taken place in the blood-pigments. If the obstruction to the blood-vessel is of slow development, which often occurs in cerebral thrombosis, the tissue is not deprived entirely of blood and a slow degeneration results, characterized by the transformation of the myelin into a granular substance and the formation of fatty particles; this gives the area a gray appearance, and it is said to be the seat of gray softening.

Emboli of various size may lodge upon the walls and induce thrombotic deposits, which soon result in occlusion of the vessel. Such emboli are frequently arrested at the bifurcation of an artery. Certain emboli of an infectious nature cause changes in the vessel-walls, and lead to aneurysmal dilatation (mycotic aneurysm). The aneurysm may be followed by thrombosis or by rupture.

At first the necrotic area produced by arterial occlusion presents a swollen, edematous appearance. Although the area of softening may be limited to one portion of the brain, such as that supplied by the lenticulostriate artery, the contents of the intracranial cavity in general may show deviations from normal. On removal of the skull-cap the veins of the diploe are in a state of congestion and the blood-vessels of the pia, particularly of the visceral pia, may be overdistended. An entire hemisphere, even when no sign of softening is apparent on naked-eye inspection, may be less consistent and more friable. If the softening involves the surface of the hemisphere, the visceral pia is infiltrated, adherent to the cortex, and devoid of its glistening, translucent appearance. Section through the softened area will reveal an appearance depending on the intensity of the process and the length of time that it has existed. If the tissue is in a state of white softening, what has already been said in regard to the genesis of this condition is sufficient to describe its general appearance. If it is in a state of red softening, the area in which tissue is undergoing destruction will present a different appearance in the center than at the periphery. In the former location there may be a complete destruction of the tissues, the only substance remaining being a semiliquid debris. This process of destruction or softening may extend in one direction from the center much further than in another, and in some cases the whole appearance may be that of a sort of cystic formation very similar to that found in an old hemorrhagic focus. The punctate hemorrhages which occur throughout the area of softening may give the necrosed tissue a cribriform or sieve-like appearance, to which particular attention has been paid by French pathologists (*"état criblé"*).

The histologic changes are similar to those that occur in any tissue undergoing noninflammatory necrosis. In white softening the striking microscopic appearance is the presence of fatty granules and granule cells.

Reparative changes similar in character to those described in cerebral apoplexy may follow any variety of softening, and these consist essentially of a cellular infiltration around the borders of the softened area, which by vascular ingrowth forms embryonic connective tissue which endeavors to obliterate the focus of softening by a process of cicatrization.

Softening of the brain due to other causes than thrombosis and embolism may occur around almost any focus of disease in the brain, be it a new growth, an inflammation, or a hemorrhage, the only peculiarity of such softenings worthy of note being that they do not confine themselves to the distribution of any single artery, but may extend into the area of a number, providing the original pressure covers such an area.

The histologic changes in the neural elements, particularly the protoplasmic prolongations of the ganglion-cells, and in the neuroglia, have been determined principally by experimentation, and they consist in the occurrence of a condition that has been called varicose atrophy in the protoplasmic processes. This begins at the termination of the protoplasmic process and progresses gradually toward the cell body. The latter may itself show chromophilic changes, and in such cases the axone becomes atrophic. It has been noted that with emboli of very fine capillary vessels those protoplasmic processes that course along the fine blood-vessels are alone the seat of the atrophic condition. The fact that changes such as these may be the anatomic basis of a few diseases like chorea, the morbid anatomy and pathology of which are still to be determined, in which capillary emboli have often been found and described, should not be forgotten.

The resulting softening constitutes the anatomic basis of a considerable proportion at least of the infantile cerebral palsies. Rupture and occlusion of cerebral blood-vessels may take place during intra-uterine life, as well as at birth and following it. In fact, such lesions are more apt to occur early than later in life.

There remains to be considered a form of brain softening associated with athrepsia, or Parrot's disease. In these cases the basis of the lesion is multiple thrombi of the pale variety in several of the very small blood-vessels, especially of the cortex, but sometimes of the white matter and of the brain ganglia. The softening that results may conform to the type of red softening or of white softening. The result is the same as in other forms of softening, except that the process is more widespread. Nothing is known of the pathogenesis of the disease; it is surmised, however, that the chronic state of malnutrition is attended by leukocytic migration and the formation of minute thrombi, causing little foci of degeneration, which in turn are followed by capillary hemorrhages. It is quite possible that some cases of porencephalus and of hydrocephalus develop in this way.

Hemorrhage and Softening in the Pons-oblongata Segment.

—Softening may follow occlusion of the arteries in the pons-oblongata segment. The histologic changes are the same as those following softening in the brain.

Cerebral Hemorrhage.—Cerebral hemorrhage or apoplexy is generally the result of disease of the walls of the vessels. Normal blood-vessels in the brain do not rupture spontaneously except when subjected to great violence. Rupture of cerebral blood-vessels is particularly apt to take place at two periods of life: in the very young and past middle age. In both cases distinct changes in the blood-vessels, the one inherited or the

result of acute infections, and the other acquired, precede the accident. The changes that favor hemorrhage are fatty degeneration of the vessel-wall and different forms of chronic arteritis, the most common being arteriosclerosis. Fatty degeneration plays a prominent part in the rupture of blood-vessels during infancy and childhood. Slight morbid changes in the blood-vessels of the unborn child may result in rupture during birth. Fatty degeneration of the cerebral blood-vessels in late adult life affects especially the small arteries. The fatty changes involve especially the muscular coat. As a result of the local weakening small dilatations or miliary aneurysms develop and subsequently rupture. Such dilatations are found in one-third to one-half of all cases of cerebral hemorrhage. Arteriosclerosis is more frequently found in the larger blood-vessels. It develops slowly, frequently in conjunction with similar changes in other parts of the body, especially in the kidney, and it generally leads to dilatation of the lumen of the vessels owing to degeneration in the media, and to fatty and calcareous changes in the thickened intima. The vessels are hard, resistant, and nonelastic, and when cut across their lumens remain patent.

Degenerative changes of a secondary nature take place in the blood-vessels of the nervous system in a great number of nervous diseases. In such diseases as tabes, syringomyelia, multiple neuritis, combined sclerosis of the spinal cord, which are attended by trophic disturbances, there are found marked degenerative changes in the blood-vessels of the nervous system.

The immediate cause of rupture of cerebral blood-vessels, whether large or small, is increase of blood-pressure or arterial tension. This may be the result of mental or physical causes. It should be borne in mind that increase in arterial tension may be relative and not absolute. The actual rupture of the vessel not infrequently takes place during sleep; but even at this time the tension may be increased relatively, especially when a contracted kidney and hypertrophied heart are present.

Hemorrhage in the substance of the brain occurs most frequently in certain areas, and especially in the brain-ganglia. The arteries of the striatum and of the thalamus, branches of the middle cerebral, rupture so much more frequently than any other that they have been called the arteries of cerebral hemorrhage. The rupture may take place in a very small branch or in a number of branches, simultaneously or consecutively, the hemorrhages coalescing to form one hemorrhagic focus which appears to be the result of a single hemorrhage. Capillary hemorrhages may occur; to the naked eye they seem like minute red specks; microscopically it is seen that the perivascular spaces are filled with the blood that has escaped from the ruptured vessels, and that the brain-tissue has been disintegrated. If the capillary hemorrhages are old, the changes in the blood and the degeneration in the brain-tissue give rise to a pale-yellowish discoloration. Capillary hemorrhages occur around larger apoplectic foci, and are then probably caused by an increase of capillary tension, the immediate result of the rupture of a large vessel. Capillary hemorrhages occur in acute hemorrhagic encephalitis, in abscess of the brain, in the infectious fevers, in delirium tremens, acute delirium, etc. Larger hemorrhages may cause death on account of the destruction of important parts, or because the amount of hemorrhage produces fatal cerebral compression; in such cases the brain will be found extensively lacerated, the convolutions flattened, the substance dry.

Immediately after rupture of a blood-vessel in the brain, secondary changes begin in the surrounding structures. Some of the changes are the result of the destruction of continuity of the neuraxones, and are of the nature of secondary degenerations, which are described elsewhere. In the motor tracts the degeneration travels downward. It is traceable to the terminal arborizations of the corticomotor neurones around the ganglion-cells in the oblongata and in the cord. Although investigations have not determined the changes in the central sensory neurones above the lesion, similar degenerations undoubtedly occur in them.

Hemorrhages in other parts of the brain than the brain-ganglia are rare. In the form known clinically as *ingravescent apoplexy*, a branch or branches of the external lenticular artery rupture, and the extravasated blood forces its way, by a process of cleavage, through the centrum semiovale into the lateral ventricles. Hemorrhage into the cortical substance that works its way toward the periphery may rupture into the intermeningeal space and cause serious compression of the brain; or there may be such destruction of the cortical substance that death takes place. Hemorrhages in the cortex may exist for a long time, and give rise to special focal symptoms depending upon the functions of the brain-area involved.

Soon after the escape of blood changes begin in the extravasation. The extravasated blood coagulates, and thus helps to close the ruptured vessel; on contracting the coagulum forces the liquid out, and this is absorbed. The clot undergoes softening and disintegration; blood-pigment is set free and tinges the surrounding structures; connective-tissue proliferation begins around the periphery of the clot, and eventually leads to the formation of a fibrous capsule. The entire coagulum may be absorbed, and all that may remain is a pigmented scar. Incomplete absorption of the clot, followed by secondary softening, may give rise to the so-called *apoplectic cyst*. In exceptional instances an old *apoplectic focus* becomes the seat of infection.

Encephalitis.—The term *encephalitis* is applied to inflammation of the brain substance. The pathology of inflammatory diseases of the brain has during the past few years been much elucidated. Formerly the subject was considered under the various forms of brain softening, and little attempt was made to discriminate the inflammatory conditions leading up to these.

Encephalitis may be classified according to its prominent pathologic feature into, first, *acute hemorrhagic encephalitis*; second, *purulent encephalitis*, *brain-abscess*; third, *interstitial* or *chronic encephalitis*. Encephalitis may also be classified according to the location of the inflammation. The constituent of the brain that manifests inflammatory phenomena most commonly is the gray matter, although any part of the brain may be the seat of the lesion. Inflammation of the gray matter, more or less localized, in different parts of the encephalon is accompanied by symptoms or by a complex of symptoms possessed of such individuality that they constitute special diseases. These diseases receive different names when different levels of gray matter are involved. For instance, acute nonpurulent or hemorrhagic encephalitis is the term applied to an acute hemorrhagic exudative inflammation of any of the constituents of the encephalon. The same variety of inflammation of the gray matter in the floor of the third ventricle and around the aqueduct of Sylvius is known as *superior acute poli-encephalitis*; while if the pathologic process involves the central gray matter beyond the aqueduct of Sylvius—in other words, that situated

around the fourth ventricle—it constitutes *inferior acute poli-encephalitis*. The last-named areas seem to have a special predilection for hemorrhagic encephalitis. In some cases the inflammatory area extends into the oblongata, or even from the gray matter of the hemispheres into the cord, the condition then being known as poli-encephalomyelitis. In short, we may say that the gray matter of the entire central nervous system may be inflamed at certain levels or planes, and that the inflammation may be limited to one of these, or the injurious substance which by its presence in the circulation of the gray matter of the nervous system calls forth an inflammatory reaction, may cause such inflammation to be manifest throughout the entire gray matter of the hemispheres and of the brain-stem, the pons, the oblongata, and the cord. The cerebellum is very rarely the seat of acute hemorrhagic encephalitis. Only a few cases have been thus far reported (von Jakseh, Fürbringer).

Clinical experience to-day teaches that this is not a fanciful division or classification. During the past ten years there have been reported in neurologic and pathologic journals a large number of cases, some of them terminating fatally, others going on to recovery or a state of chronicity, which have pointed unerringly to the reality of poli-encephalomyelitis. Even though the microscopic examination of the cases that have come to autopsy has not completely corroborated such classification, we would still be obliged to admit on clinical grounds the occurrence of such conditions. Cases of anterior poliomyelitis associated with involvement of nerve-nuclei which have their seat in the pons and oblongata indicate unequivocally a lesion of the gray matter in three different levels or segments of the central nervous system. In the same way symptoms of acute hemorrhagic encephalitis associated with pontile and bulbar symptoms point to widespread involvement of the gray matter.

Another very important link in the chain of evidence that is being forged around this class of diseases is, that they are all practically due to similar causes. Acute hemorrhagic encephalitis, poli-encephalitis superior and inferior, bulbomyelitis, and anterior poliomyelitis, all occur in the wake of infectious diseases, all occur as a manifestation of some toxic substance, perhaps a specific microbe, circulating in the system. In one instance the toxic substance manifests its destructive action on one part, in another instance on another, and in a third on the entire central nervous system.

Acute Hemorrhagic Encephalitis.—The essential pathologic condition is an acute inflammatory process in the blood-vessels of the brain. The lesion consists of intense hyperemia, hemorrhagic exudation, leukocytal infiltration, and multiple small hemorrhages. The lesion is generally focal, single or multiple, but it may be widely distributed and involve a considerable part of one entire hemisphere, or circumscribed more or less symmetric areas. The predilection of certain areas of the central gray matter for this form of inflammation has been mentioned. In a number of cases the motor area of the cortex seems to be the favorite seat of the lesion. The temporal lobes, the base of the brain, and the striatum may be the regions of profoundest involvement. The inflammatory foci vary from a size so small that they are recognizable only on microscopic examination, up to involvement of a large part of a hemisphere or the basal ganglia.

The changes in the meninges will depend upon whether or not the hemorrhagic encephalitis occurs concomitantly or associated with such conditions as meningitis, thrombosis of the lateral sinus, etc., as it occasionally

does. In the latter case the morbid conditions constituting these diseases are apparent. If the acute hemorrhagic encephalitis occurs apart from any involvement of these structures, following some of the infectious diseases, such as influenza, scarlet fever, etc., the coverings of the brain may present a completely normal appearance. Usually their blood-vessels are distended, and often the pia is cloudy. The visceral pia is not infrequently hyperemic, especially in the vicinity of the inflammatory area, and when stripped from the cortex leaves numerous spots of punctate extravasation. When the inflammation is of the cortex the pia is always involved. The encephalon itself, or at least the parts of it that are diseased, is red and swollen, the normal differentiation between the gray and the white matter is obscured, and to the naked eye it has a peculiar stippled appearance. The variation of color depends on the amount of hyperemia and hemorrhage, the extent to which the extravasations have penetrated the brain substance, and the intensity of the resulting destruction of the latter. To the touch the tissue is less resistant, and in some instances it is almost pultaceous. The hemorrhages vary in size from that of a pin-point up to as large as that of the end of a pencil. When the ventricles are laid open they are almost always found to contain an increase of fluid. The larger blood-vessels are almost invariably intact. Microscopic examination shows a large number of small vessels ruptured, others distended. Around the unruptured vessels in the inflamed area is well-marked evidence of perivascularitis, and, if the inflammatory process has been of some duration and considerable severity, small foci of degeneration, particularly around the ruptured vessels, can be observed. These foci are made up of granular cells constituted of leukocytes filled with myelin substance and other debris. Round-cell infiltration, not alone of the vessel-walls, but throughout the inflamed area, is present. Occasionally a marked nuclear proliferation in the vessel-walls has been found (Buckler); while in other rare instances there is fatty degeneration of the walls of the vessels (Nauwerck). If the inflammatory process has been a less severe one and of slower progress, one of the most constant features recognizable with the microscope is an increase in the number of spider-cells, the so-called cells of Deiters. These cells undergo not only increase in size, but their nuclei and bodies also undergo a change which allows them to absorb pigment-stains more intensely than is natural.

Some cases of acute hemorrhagic encephalitis terminate in complete recovery. It is not impossible that the small reparative or cicatricial foci which remain after such a mild type of encephalitis may be the starting point of a new disease-process later in life, and that tumors may take their origin from the seat of, and perhaps be in some way influenced in their development by, these inflammatory foci of ancient date. In this way may be explained the known relationship of trauma and cerebral tumors. It is possible also that the genesis of cerebral lesions of disseminated sclerosis may be related to a previous encephalitis.

The changes that go on in the ganglion-cells of areas of the brain which are the seat of hemorrhagic encephalitis are only now beginning to be recognized. In some instances the lesion of the cells is very slight; in others it is most destructive. Changes analogous to them have been studied in cases of experimental encephalitis and in cases of acute hemorrhagic encephalitis due to sunstroke. The Nissl method of staining has shown that decided changes go on in the protoplasmic substance and in the internal structure

of the cell-body. The chromatic substance of the cell-body takes up the methylene-blue stain with great intenseness. The chromatic part is represented by numerous spots or chains of distinct blue granules, the whole giving an irregularly spotted or tiger-hide-like appearance of the cell-body. *A priori*, ganglion-cells that show changes of this kind should be accompanied by degeneration of their neuraxones, and it is very likely that they are, but histologic technic at the present day will not reveal them. All the

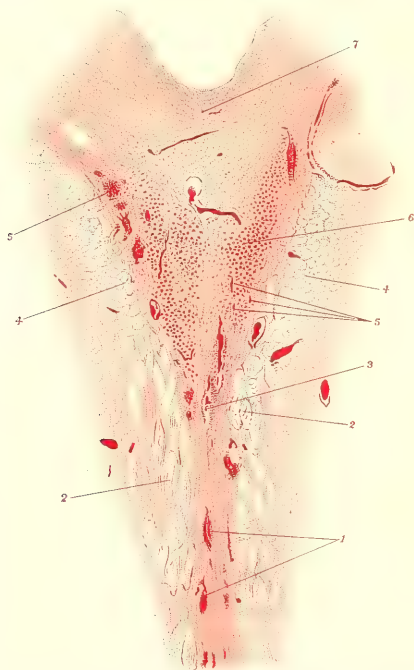


FIG. 200.—1, Blood-vessel passing in median line to the region of the oculomotor nucleus; 2, root-fibers of the third nerve; 3, (vessel) space with free blood-corpuscles; 4, posterior longitudinal bundle; 5, free hemorrhage; 6, anterior oculomotor nucleus; 7, cerebral gray matter (Boedeker).

processes of the ganglion-cells in an inflammatory focus are more or less shrivelled, atrophied, and stunted. Sections stained according to the method of van Gieson, or with carmin-stains, reveal the degenerative changes in the cell-body and the nucleus. The cells may have a hyaline appearance, or they may show simple fatty or calcareous degeneration. Often there is to be seen in the immediate vicinity of a cell a thin layer of pigment-deposit. When the inflammatory process is of such severity as to lead to local necrosis or softening, the histologic findings consist of the débris of the constituents of the part.

Acute hemorrhagic encephalitis, like acute poliomyelitis, is primarily a disease of the blood-vessels, with secondary involvement of the ganglion-cells; or perhaps it might better be said that the injurious agencies act on the ganglion-cells through the mediation of the blood-vessels. Certain intoxications (alcohol), sunstroke, etc., have a special affinity for the ganglion-cells of the cortex and the central ganglionic masses, but they reach these through the vascular system, and exercise a preceding or coincident effect upon the latter.

Acute Poliencephalitis Superior.—This constitutes a clinical entity. The anatomic basis of the disease is an acute hemorrhagic inflammation of the gray matter in the floor of the third ventricle and the aqueduct of Sylvius. For a time it was supposed to be dependent upon a single cause, namely, chronic alcoholism. It has been shown recently that it also occurs as a sequel of acute infectious diseases and after poisoning by mineral substances, such as sulphuric acid, lead, and carbon dioxid. The pathogenesis of the lesion is that of any acute hemorrhagic exudative inflammation occurring in the gray matter, and it does not call for separate description.

Section through the brain reveals the gray substance around the walls of the third ventricle for a variable distance to be of a dark rose-red color, of a pulaceous consistence, and the seat of numerous punctate hemorrhages and hemorrhagic extravasations. Occasionally the hemorrhages or hemorrhagic foci extend as far as the posterior quadrigeminal body and the posterior commissure, in the peduncles and pons, and may be traced to the beginning of the fourth ventricle. The blood-vessels in other parts of the brain are, as a rule, normal, but they may be in a state of degeneration.

A similar pathologic condition may occur around the upper part of the fourth ventricle in the substance of the gray matter there situated, and cause symptoms referable particularly to the tenth and the twelfth cranial nerves. This condition is called poliencephalitis inferior, and it is due to similar causes as the superior form, and the pathologic changes are the same.

Occasionally the lesion extends into the gray matter of the oblongata, particularly the ventral gray matter, thus constituting bulbar poliomyelitis. The inflammation in this condition is not always of a hemorrhagic nature, but may vary from the slightest states of exudative inflammation to an acute inflammation with necrosis.

Purulent Encephalitis.—Purulent encephalitis is the result of the activity of pyogenic organisms (the *Staphylococcus pyogenes aureus*, the *Streptococcus pyogenes*, the gonococcus, the *Diplococcus pneumoniae*, and a number of others) on the tissues of the brain. If the inflammatory process is circumscribed and the collection of pus limited, it is called *brain-abscess*. Such abscesses occur in two forms: the first, acute non-encapsulated abscess, generally situated in the interior of the brain, composed of an irregular cavity containing pus and the débris of brain-tissue; the second, of a chronic encapsulated abscess formed of a regular cavity surrounded by a layer of dense connective tissue, containing pus in various stages of degeneration.

The location of brain-abscess stands in rather close relationship to the factors that cause the abscess. These factors are, first, chronic suppurative disease of the middle ear, to which about 35 per cent. of all cases of brain-abscess are traceable; second, trauma, which is responsible for a large number of brain-abscesses; third, suppurative process in any of the cavities

or sinuses of the skull, such as the nasopharynx, which are in close communication directly or indirectly with the contents of the skull ; purulent disease of the frontal and ethmoid sinuses, the orbital cavity, etc. ; fourth, metastasis of pyogenic organisms from a distance, such as from bronchial dilatation, subacute pneumonia, pulmonary phthisis, empyema, gangrene of the lungs, and endocarditis. This latter group make up about one-fourth of the whole number. The foci of purulent inflammation in the brain that occur with pyemia are considered a part of that disease, and not of brain-abscess.

Abscesses of the brain are found more often on the right side than on the left, and abscesses due to disease of the middle ear are generally situated on the same side as is the purulent process from which they originate, and in the vast majority of cases either in the temporosphenoid lobes or in the cerebellum. Abscesses due to trauma may occur on the side of the brain which has been the seat of the original injury, but it is quite as common for them to occur on the opposite side. Traumatic brain-abscess is more liable to be situated superficially and to be located in the poles or superior surface of the brain than are other forms. Metastatic brain-abscesses have a predilection to occur in an area supplied by the artery of the fissure of Sylvius on the left side, and in the central ganglia and midbrain. Abscess of the brain is generally single, and varies in size from that of the end of a finger to that of a closed hand. Abscesses are sometimes multiple, the different abscess-cavities being of varying size, and the foci of suppuration have no connection one with the other.

It depends upon the rapidity with which the purulent process develops, and upon the duration of the disease, whether or not the abscess will have a limiting membrane ; that is, be encapsulated. If the process has developed rapidly and is of moderately short duration, there will be no surrounding abscess-wall. The process of inflammation may be traced through various stages of transition from the center of the abscess-cavity, where the contents are entirely purulent, toward the periphery through various stages of inflammatory reaction. When such abscesses occur in the cortex, they are often associated with diffuse purulent leptomeningitis. Abscess of the temporosphenoidal lobes or of the cerebellum secondary to purulent middle-ear disease are often accompanied by implication of the dura between the abscess-cavity and the middle ear. In such cases the pathway of infection is very evident. In those cases in which there is healthy brain-tissue between the temporosphenoid abscess and the bone infection takes place either through the veins that enter the superior petrosal sinus or through the perivascular lymphatics ; and in such cases there is sometimes found thrombosis of the veins and sinuses, thus establishing a direct communication between the focus of original affection and the abscess, or there may be found a purulent infiltration following the course of the seventh pair of nerves.

Brain-abscesses of slow development and considerable duration are provided with a limiting membrane which encapsulates the pus. The histogenesis of this membrane is the same as that of other limiting membranes. By virtue of such encapsulation small abscesses, and even abscesses of considerable size, may for years exist dormant and symptomless in the brain. In years after its occurrence, either as the result of trauma or from a process of pressure and attrition, the surrounding barrier may give way

and the contents of the abscess-cavity rupture into the lateral ventricles on the surface of a hemisphere or into the substance of the brain. In such cases a chronic abscess may appear in the guise of an acute one, but bacteriologic and histologic examination of the pus will show wherein it differs from that found in acute abscess. It has been demonstrated beyond cavil that pus may become sterile in old-standing collections which have no communication with the external world. In such encapsulations the microbes first lose their virulency, and, although still able to grow on media, they have lost the power to overcome the resistance offered by living tissues or organisms. Finally they lose their vitality, and eventually become completely disintegrated.

The fact that the limiting membrane which encapsulates a brain-abscess is sometimes sufficient to bring the activity of purulent collections to an end is shown by records of cases in which abscesses firmly encapsulated are found in the brains of those dying from other diseases. The physical characters of the abscess-cavity and its contents need no description. Like abscesses in every other part of the body, these vary with the rapidity and profundity of destruction and the presence or absence of organisms, like the *Bacillus pyocyaneus*, which lend easily detectable attributes to any substance to which they have entrance.

The tissues of the brain in the vicinity of an abscess are the seat of pathologic changes. In the case of acute abscesses these are very pronounced; in chronic abscesses, especially those of long duration, in which the delimiting membrane is firmly developed, they may be entirely lacking. In acute abscess the environmental area is found in different stages of hyperemia and infiltration dependent upon the rapidity of the abscess formation and the destructiveness of the process. Microscopically the peripurulent area shows transitory changes in the blood-vessels, perivascular spaces, and integral tissue, which vary from those common to minor degrees of inflammation up to the normal.

Abscess may occur in one part of the brain, and the characteristic lesion of hemorrhagic encephalitis in another. It has been contended by some that both of these morbid processes are the expression of reaction to the same morbid agency, the one in which there is greatest tissue destruction indicating the activity of the agency while possessed of its virulency; the other the activity of the injurious agency after its virulency is spent. At least, it can be positively stated that the same coccus, the pneumococcus, for instance, causes hemorrhagic encephalitis in one instance and purulent encephalitis in the next.

An encephalon that contains an abscess usually presents abnormalities detectable as soon as the calvaria is removed. Some of these are dependent upon the conditions that are directly causative of the abscess, such as evidences and sequences of trauma, middle- and internal-ear disease, etc., manifest in the bones of the skull, the membranes of the brain and their contents, the vessels and sinuses. Thus, there may be erosions or injury of bone, extradural collections of pus, sinus-thrombosis, purulent meningitis, subdural and intermeningeal hemorrhage. Even when the abscess-cavity is deeply situated in the brain substance, the meningeal and cortical vessels are somewhat congested. The part of the encephalon the seat of the purulent collection is likely to be somewhat bulging, or the only revelation of its presence before section of the part may be a diminished consistency approach-

ing semifluctuation. Around ancient collections of pus the brain-matter may be of exceptional paleness; in fact, just around such a collection it may be the seat of slow degeneration, constituting an area of so-called white softening, while around the acute abscess there is an area of red softening.

Interstitial or Chronic Encephalitis.—The pathology of chronic interstitial encephalitis is one of the most obscure problems in neuropathology. It is a relatively uncommon condition, occurring as a separate disease, with which are associated certain symptoms. Chronic interstitial encephalitis occurs, first, as a diffuse process which may involve the entire brain, one hemisphere, or a part of a hemisphere, leading to atrophy or to hyperplasia; second, it may occur in limited and circumscribed areas as a terminal stage of other conditions, for instance, in inherited syphilis in infants, around congenital and acquired defects, such as porencephalia; third, sclerosis of the brain may be sequential to acute nonpurulent encephalitis; fourth, it may be the lesion of one form of syphilis of the nervous system, syphilitic degeneration of the hemispheres; fifth, tuberculous inflammation of the brain substance may result in the formation of certain circumscribed masses of embryonal tissue which constitute a form of chronic encephalitis; sixth, a degeneration of the cortex, especially of the anterior pole and motor regions of the brain, occurs with chronic degenerative chorea, which I shall have to refer to; lastly, islets of sclerosis, which constitute the disease multiple or disseminated sclerosis, are distributed throughout the entire central nervous system, and a number of them may have their seat in the encephalon. This form of sclerosis is not considered in this book as a variety of interstitial encephalitis, and consideration of its pathology will be given under a separate caption.

Diffuse sclerosis of the brain consists of an increase in the sustentacular tissues of the brain, the connective tissue, and the neuroglia, and an atrophy of the parenchyma of the brain, the nerve-cells and their prolongations. The histologic abnormalities are not, however, limited to these structures, for in nearly every case there are unmistakable evidences of previous inflammation or degeneration in the blood-vessels. The atrophy of the nerve substance is accompanied by the development of amylaceous bodies and Gluge's corpuscles in considerable numbers. In all cases there is an increase in the consistency of the diseased areas, and in many cases diminution in size, although some instances of what may be termed hypertrophic sclerosis have been reported. If the sclerosis is very extensive the brain, as it lies *in situ*, after the removal of the calvaria, may be separated from the dura by a space of half an inch. The brain usually preserves its normal contour. The pia is often adherent, and after it is detached the sulci and fissures seem widely separated and gaping. After the pia is removed the brain does not alter its shape or fluctuate as its position is changed, nor does it on handling. On cross-section the leather-like consistence resists the knife, which passes through it with a creaking sound. When the ventricles are opened they are found enlarged, a change that is more apparent than real, on account of the consistence of their walls. The sclerosis resulting from chronic encephalitis may be of a hyaline nature or character, which on microscopic examination is found to consist of hyaline degenerated blood-vessels and connective tissue. Such conditions are most commonly found in the brain of chronic demented. The process may be limited to a definitely circumscribed area.

The white substance is the principal seat of the sclerosis, although the cortical substance is thinned and of an atrophic appearance. In the cases occurring in young children affected with inherited syphilis the gray matter is more distinctly the seat of the sclerosis, which is sometimes limited to one or more convolutions. In many cases of sclerosis of the brain there is a degree of compensatory hydrocephalus.

In the cases of diffuse sclerosis which follow acute nonpurulent encephalitis, the lesion of the nerve-matter is associated with vascular changes as well as with increase of connective tissue. The atrophy and sclerosis in these cases are of much wider extent, in all probability, than the original inflammatory process. The degree of such atrophy may be so advanced that the cortex becomes absolutely unrecognizable as such, being devoid of all trace of nerve-structure, and consisting only of condensed neuroglia and post-inflammatory and degenerative sclerosis. The causation of diffuse or local sclerosis of the brain is as obscure as the pathology. In the syphilitic and the tuberculous forms the specific factor of these diseases is responsible. In many cases of the diffuse form no etiologic factor save alcoholism and associate sclerotic change in the hematopoietic organs can be made out.

Chronic Degenerative Chorea (Huntington).—The anatomic basis of chronic degenerative chorea (Huntington's chorea) may be considered a degenerative disease of the cerebral cortex. The morbid anatomy of this disease is now fairly well established. There may be some hesitancy in admitting the disease to the category of encephalitis, as in reality the disease is a teratologic defect of the ganglion-cells, the changes in the mesoblastic structures being secondary and dependent. The ganglion-cells in individuals who develop Huntington's chorea are endowed with specific energy or vitality to enable them to exist only a certain length of time, although it should be understood that they have the full potentiality of development, and the possessor may have enjoyed the fullest complement of mental development before the period of decay is at hand. It is referred to here as a matter of convenience, and without desire to place it in the category of inflammations.

Evidences of disease in the brain of a case of Huntington's chorea are both macroscopic and microscopic. The changes are most apparent—indeed, it may be said they are confined—to the frontal and central regions of the brain: the areas that subserve intellection and movement. The convolutions are less prominent than normal, oftentimes distinctly atrophied. Not infrequently there are seen anomalies of fissuration, usually some defect. As in every other form of chronic degenerative disease of nervous structure, the meninges are thickened and degenerated, especially in patches, the blood-vessels senile; but there is nothing characteristic or suggestive of the disease in these lesions.

In rare instances pachymeningitis interna hæmorrhagica has been found. This occurs only in cases of prolonged and pronounced convolitional atrophy. On cross-section the mantle of gray matter is considerably thinner than normal, and on microscopic examination this thinness is recognized to be the result of degeneration and shrinkage of the ganglion-cells of the part, especially of the layers of the small and large pyramids. Sections stained by the Nissl method show the characteristic changes of slow degeneration both in the cell-body and in the nucleus, while the processes are disintegrated. The

cell-body is frequently granular, and the nucleus prominent and enlarged or scarcely recognizable. The tangential fibers show evidence of decay. The perivascular spaces are enlarged, in some areas pronouncedly, and in the immediate vicinity of these areas a considerable number of scavenger-cells is seen. The blood-vessels are slightly thickened, especially in scattered foci; and, in areas in which this thickening is most pronounced, there is some round-cell infiltration. Blood-vessels cut longitudinally show this condition better than vessels cut across.

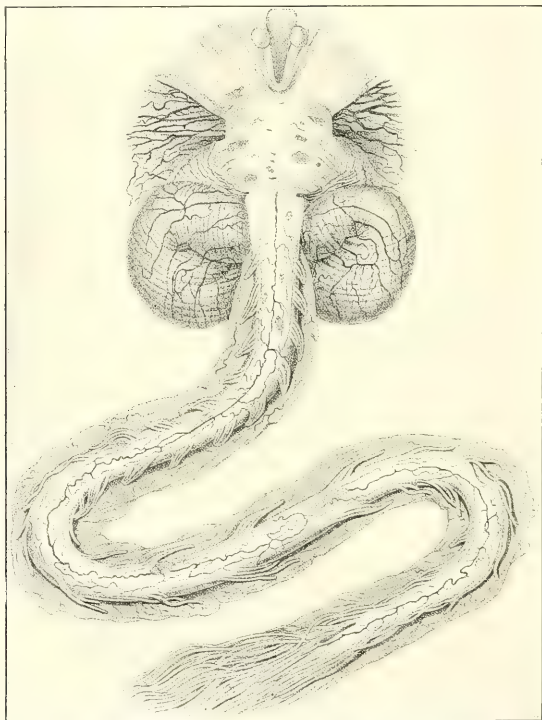


FIG. 201.—Typical case of disseminated sclerosis of the spinal cord and midbrain (Leyden).

In cases of long standing, secondary changes in the pyramidal projections of the cord are detectable on application of the Weigert method of staining, and, if the degenerative process has not been completed, by the application of the Marchi method.

Multiple Sclerosis.—The morbid changes of multiple or disseminated sclerosis consist in gray foci or patches of sclerosis, of varying histologic constitution, found irregularly distributed throughout the entire central

nervous system. In some cases these patches predominate in the cord, while in others the brain is almost exclusively the seat of lesions. Formerly it was believed that the islets of sclerosis were limited in their distribution to the white matter. It is now recognizable that this is not true, although the white matter is the seat of the foci somewhat oftener than the gray.

In the brain the islets, varying in size from that of a pin-head up to two or three inches in diameter, may be adherent to the pia, or they may be first seen after the meninges have been removed and the brain substance cut into. When they are situated superficially in the cortex the transparent pia allows them to shine through before it is stripped off; and if they are of considerable size, which they are not likely to be here, the pia may be irregularly elevated over them. On cross-section of the hemispheres one readily appreciates the increased resistance to the knife as it passes through sclerotic foci. The tissues adjacent to the lateral ventricles seem to have a special predilection for the development of large-sized foci. Section through the midbrain, the basal ganglia, the pons, and the oblongata shows the grayish, slate-colored, or grayish-red patches encroaching upon or usurping entire areas or segments. In the pons and oblongata particularly the foci of sclerosis are sometimes of comparatively great size. In other instances the islets involve some of the cranial nerves; the second being particularly liable to such involvement, either in its extracerebral or intracerebral course.

In the spinal cord the islets may be situated in any level from the oblongata to the cauda equina. The cervical and lumbar enlargements seem to be favorite seats. The irregularity and bizarre manner in which the lesions are scattered are the most distinguishing feature. In one level they may involve the anterior columns, at another the posterior, while at another any combination of either these two with involvement of the lateral column or involvement of the lateral column alone may exist. The islets of sclerosis, especially the larger ones, are apt to be situated in the white matter of the cord, while those of smaller size are found in the gray matter, and not infrequently these are microscopic.

The disseminated foci or islets of sclerosis are usually of a rounded, lenticular, more or less irregular shape, sharply differentiated from the surrounding tissues, both by consistence and color, although the latter is less obvious when the islets develop in the white matter. In their distribution they seem to be entirely without order, and without relation to nerve-tracts or individual nerve-structures. This is suggestive that the islets are in relation to distribution of the blood-vessels, and the recent contributions of Demange, Ribbert, and Dejerine tend to substantiate this view. To the naked eye the islet seems of uniform structure unless rapid disintegration is going on in the nerve-fibers that penetrate it, when the myelin and fat and the degenerated fatty cells and fat-granule cells may give it a slightly variegated appearance. These conditions are readily recognized by the microscope, which shows the islet to be made up of connective tissue and of neuroglia and of the neural elements in which the sclerotic patch has developed. If it be situated in the white matter, the axones are seen passing through the mass of foreign tissue, and between them and the latter there is a variable amount of glia-tissue; in other words, they have been robbed of their medullary sheaths. In some instances the nerve-fiber has entirely disappeared, probably in the manner indicated above, and the space previously occupied

by it is readily apparent. These spaces and degenerated nerve-fibers are most often encountered toward the periphery of a patch where granular and amyloid bodies, drops of myelin and fat, and granule-cells are seen in greatest number.

The changes in the blood-vessels are by no means constant nor characteristic. In some cases, perhaps the majority, distinct vascular lesions in the shape of thickening of the walls, hyaline degeneration, and increased perivascular distention are found. In exceptional instances multiple thrombosis of capillary vessels has been noted.

The changes in the neuroglia in cases of multiple sclerosis are likewise inconstant. In some instances there is a marked increase in glia-tissue, and the development of this neuroglia seems to be at the expense of the parenchyma. This form is likely to be found in the spinal cord, especially in the gray matter and the posterior columns, and in the center of the brain in the vicinity of the ventricles, locations at which glia-tissue is normally most abundant. In other cases the neuroglia is slightly increased, the sclerosis being constituted of connective tissue in different stages of development and the degenerated parenchyma, including the diseased blood-vessels in which it is situated.

Little is known of the causation of multiple sclerosis. But it seems to be rather generally admitted that the disease develops in the wake of the infectious and toxic diseases with or without intermediate clinical manifestations of acute focal encephalitis, myelitis, or encephalomyelitis, and in other cases there is a distinct hereditary or family history which has led to the belief that the disease is one of defective embryonal evolution. These two forms of the disease, etiologically considered, would seem to harmonize in a measure with the different histologic make-up of the multiple lesions. It is possible that the form of the disease which develops from some defective evolution antedating birth corresponds to those in which the neuroglia is found increased. On the other hand, it is not improbable that in those cases in which the lesion histologically is parenchymatous degeneration of the neural constituents in which the focus is developed and a reaction of the mesodermal elements of the part to the injurious agency, the disease in reality is the terminal one of a parenchymatous degeneration which may have been in the beginning acute, subacute, or chronic. This view would in a measure reconcile the diverse opinions that have been held concerning the pathogenesis of the disease. Those who teach that there is a primary disease of the neuroglia, as well as those who claim a primary disease of the blood-vessels, both have their claims allowed, particularly if the latter do not hold too closely to the view of Rindfleisch and others, that the sclerotic process beginning in the perivascular spaces gradually implicates the surrounding tissue and causes atrophy and destruction of the nerve-elements, but assume rather a parenchymatous disease associated with, or possibly dependent upon, affection of the small blood-vessels. According to this latter view, there may or may not be considerable proliferation of connective tissue. If the process has been a very slow one, in all probability there will be such development; but if it has not, there will be very little genuine sclerosis, the appearance of sclerosis being given by the presence of the degenerated neural elements which lie between the persisting nerve-fibers.

This conception of the pathogenesis of the disease is more in harmony with its etiology and course, and is more reconcilable with the principles of

cytology and pathology, particularly those governing the process of neural destruction and repair, than any other that has been propounded.

Progressive General Paralysis; Paralytic Dementia; General Paralysis of the Insane.—Progressive general paralysis is one of the few mental diseases that are accompanied by detectable anatomic changes in the nervous system. The lesions are distributed throughout the entire nervous system, central and peripheral. Pathologists are not in accord as to what the original nature of the lesion is, although there is unanimity that the process leads eventually to atrophy of the brain. Formerly it was believed that this atrophy was of inflammatory origin, the pathologic process being indicated by such designations as parenchymatous encephalitis, cortical interstitial encephalitis, chronic meningitis with associated and consecutive involvement of the cortex, etc. Latterly there would seem to be a consensus of opinion to the view that the process is a primary simple atrophy. Previous syphilis is by far the most important etiologic factor—there is a history of syphilis in 85 to 95 per cent. of the cases—yet the pathologic changes are not of a syphilitic nature. Although such extensive lesions are not found in any other disease of the nervous system, yet lesions of the same general character may be produced by other conditions.

The changes in the central nervous system and its coverings are often apparent to the naked eye. The dura is frequently adherent to the skull, and is the seat of internal hemorrhagic pachymeningitis. This condition is more frequent in the dura of the convexity, although it may extend to the base and even into the spinal canal. The pia is often cloudy and thickened, especially over the anterior pole of the brain. The thickening of the pia may be apparent by the presence of whitish streaks or bands along the course of the veins, or it may be diffuse. There is proliferation of endothelium on the inner surface of the visceral pia, which unites with the cortex by adhesions frequently so firm that the cortex is torn in endeavoring to strip off the pia. Microscopically the vessels of the pia are seen to be surrounded by small-cell infiltration. The encephalon is occasionally of greater volume than normal, this being due to an internal hydrocephalus. When the pia is removed the convolutions are often less well marked than normally, and on section into the brain the substance is of an abnormal pallor and the cortical mantle distinctly thinned. The vascular changes in the brain are often recognizable by the naked eye. They give rise to a porosity, or sort of cribriform state, due to distention of the vessels and enlargement of the perivascular spaces. Section into the ventricles rarely fails to show the latter enlarged, and the ependyma and choroid plexus are the seat of granulations. The basal ganglia, pons, and oblongata, and also the cerebellum, are not usually the seat of changes recognizable with the naked eye, although the meninges may be thickened over the last. On removal of the spinal cord, marked adhesion of the pia, especially over the posterior columns, may be found, and cross-section of the cord in its fresh state often reveals changes in the posterior columns. The peripheral nerves are paler in color than normally.

Microscopic examination of the brain, especially of the frontal region, shows decided changes in the neurocytes, their protoplasmic prolongations, and axones. The neuroglia is very much increased. Although these changes are most marked anteriorly to the central fissure, they are not wanting in the cortex posterior to this. The lesions of the neurocytes are

best revealed in sections stained with methylene-blue or anilin-blue-black. There are swelling and cloudiness of the cell-body, and in a later stage shrinkage and atrophy of its protoplasm, with granular formations, which stain deeply. The nucleus refuses to stain deeply. Pigmentation and vacuolation are present. The neuraxones are changed in contour and size, while the dendrites are stunted and shrunken. When the nerve-fibers are stained so as to bring out the medullary sheath, it is seen that the latter has in part or entirely disappeared. It has been pointed out by many writers that degeneration of the radiating and longitudinal fibers of the cortex is one of the first lesions produced by the disease.

Sections of the cortex stained according to the Mallory or Weigert neuroglia method show striking changes in the neuroglia. The nuclei of the glia-tissue are increased in number. The increase of glia-tissue is associated with an increase of connective tissue which grows in from the pial prolongations. In advanced cases the connective-tissue changes, associated as they are with well-marked degeneration of the blood-vessels with thickening of the vessel-walls, proliferation in the adventitia, dilatation of the lumen of the vessels and of the perivascular lymph-spaces, give the appearance of a primary sclerosis. This is most striking in the cortex; taken in connection with the thickening and degeneration of the pia, they have given rise to the view that the essential lesion is a meningo-encephalitis. It is to be remembered, however, that the changes in the blood-vessels, although well marked, have nothing specific about them, and are exactly such as are seen in blood-vessels of any part of the nervous system the seat of degeneration. So far as we are able to judge from the results of examination of the terminal conditions in general paralysis, it would seem that the change is primarily in the neurocytes of the cortex, followed by changes in the supporting tissue; in short, the lesion is primarily parenchymatous, and secondarily interstitial.

The changes of combined systemic disease often occur in the cord, the lesions involving the posterior and the lateral columns. In other instances the spinal degeneration confines itself to the posterior columns, and is in no way different from that in *tabes dorsalis*. In cases of this kind some writers believe that the tabic manifestations preceded the paretic, and that the disease was in the beginning a *tabes*, to which had been superadded extensive degeneration of the nervous system. Two forms of degeneration of the posterior columns in progressive paralysis have been differentiated by Marie. The first, a degeneration of the posterior column, the posterior roots being intact, a condition which he calls *endogenous*, and which is always associated with degeneration in the lateral column. The second form, of *exogenous* character, is one in which the posterior roots are primarily degenerated, and the lesions are predominantly of the column of Lissauer and the external part of the column of Burdach. When the lesions in the spinal cord conform to the type of combined sclerosis, the tracts affected may be traced as in secondary degeneration throughout their entire length. Examination of the peripheral nerves and of the cranial nerves often shows degeneration of these structures.

Syphilitic Encephalitis.—Syphilitic encephalitis consists of gummatous formations in the gray and the white substance of the cerebral hemispheres, especially in the gray matter. Syphilis of the nervous system always develops in the connective-tissue structures, and the starting point

of the diffuse round-cell infiltration in this condition is from the tela choroidea and the blood-vessels. The diffuse or nodular proliferation undergoes retrograde changes, hyaline degeneration of the vessels, and caseation of the cells. In the circumscribed form atrophic cicatrization often takes place; this results in little areas of sclerosis, giving the patches and their surroundings a striking appearance, with a grayish-white or yellow center and grayish-red periphery. Occasionally this reminds one of multiple sclerosis, and, when circumscribed syphilitic encephalitis is the only manifestation of syphilis of the nervous system, it may be quite impossible to distinguish it from disseminated sclerosis. For further details concerning syphilis, see section on Meningitis.

Actinomycosis.—There exists but one observation of an apparently primary actinomycotic process in the central nervous system, namely, Bollinger's. There was in his case an oval swelling as large as a hazelnut growing into the third ventricle between the pillars of the fornix. The growth consisted of lymphoid and larger cells, and characteristic granules in all stages of development.

Actinomycosis may invade the cranial and spinal contents either by progressive extension from cervicofacial, retropharyngeal, and retro-esophageal foci, or by way of metastases through the blood-vessels. Of 19 cases collected by Poncet and Bérard, 8 belong to the former and 11 to the latter group. In cases of direct extension the process makes its way along the foramina and canals, more rarely by perforation of the bony wall. The resulting meningitis may be local or diffuse; in some of the latter cases there has been mixed infection. The characteristic yellowish, gray, and speckled actinomycotic infiltrations may be associated with serous and fibrinous exudate, and granules may float free in the exudate. In old cases there may be firm adhesions between the membranes. From the leptomeninges the infiltration may extend into the underlying structures. Craniomeningeal actinomycosis has a tendency to invade the walls of veins and sinuses.

Metastatic actinomycosis of the central nervous system is usually part and parcel of the pyemic form of the disease. The secondary foci may assume a neoplastic type without distinct suppuration, being composed of gelatinous tissue; actinomycotic abscesses, however, are more frequent, and they may be single or multiple, deep or subcortical and superficial. In the case of the spinal cord, compression may result from invasion of the spinal canal and membranes.

Eppinger, Sabrazes, and Riviere have described leptomeningitis and cerebral abscesses due to certain forms of streptothrix (atypical ray-fungi). The *Oidium albicans* or thrush-fungus has also been found in the brain as a result of metastatic processes.

Tumors of the Brain.—Tumors of the brain are, with the single exception of glioma, not unlike those in other parts of the body, and as the subject of tumors is considered extensively in another chapter, description here will be confined to general remarks concerning the causation, the size, the distribution, and the peculiarities as determined by location. Those that are developed from the membranes of the brain directly and those that are developed from the bones of the skull are spoken of in the chapters devoted to these respective conditions. Most tumors, with the exception of glioma, develop in the meningeal prolongations which extend into the substance of

the brain ; but naturally tumors beginning thus are not classified as tumors of the meninges.

There are four forms of tumor of the brain that are of great importance because of their frequency and because they constitute almost all of the intracranial new growths. These four are glioma, tubercle, gumma, and sarcoma. In addition to these there are found occasionally carcinoma, neuroma (which is extremely rare), myxoma, lipoma, osteoma, cholesteatoma, and angioma. Under the heading of Tumors of the Brain, parasitic cysts must be included, because clinically they produce phenomena strikingly similar to those of other forms of tumor.

Tumors of the brain are liable to occur at any age from earliest infancy to senility. The vast majority of cases of tumors that develop before adult life are of a tuberculous or gliomatous nature ; the majority of those occurring after adult life are gummatous and sarcomatous, although glioma is not an uncommon form of neoplasm in adult life ; and carcinoma, a rare form of tumor formation, occurs only in adult life, being always secondary to carcinoma elsewhere in the body.

An etiologic factor of brain-tumor, the mode of operation of which can only be suspected, but which plays a most important role if we may judge from the frequency with which it has been noted to precede the occurrence of brain-tumor, is trauma. A number of hypotheses have been formulated to explain this relationship, some of these fitting in with Cohnheim's idea that tumors develop from embryonal remnants in the tissues, and others with Virchow's, that tumors are from connective tissue which the trauma caused to proliferate, but none of the hypotheses so far has been capable of scientific demonstration. The fact that trauma enters into the causation explains the greater frequency with which these conditions are seen in the male sex. The causes of parasitic tumors are the ova of the echinococcus. Tuberculous tumors are very often multiple, and have a special predilection for the cerebellum, the base of the brain, and the basal ganglia. Next in point of frequency after the cerebellum and the brain axis as a location for tumor come the cortex and the centrum ovale. The tumors occurring in these locations are sarcoma, carcinoma, and glioma, and the parasitic or cystic tumors are also liable to be situated in the cortex. Glioma may be found in any part of the brain, but it seems to have a predilection for the cortex and for the pons and oblongata. Gummatous tumors are more frequent at the base and in the brain-axis than in any other part, although they may have their seat in the cortex.

Glioma.—This form of tumor is peculiar to the nervous system, and occurs only in the latter and such prolongations of it as the retina. It is one of the tumors that are frequently seen in childhood and early adult life, and may be found in any part of the central nervous system. As a rule, it is solitary, and of a size varying from that of the end of the finger to that of a closed fist. It is very vascular, and on that account grayish red or reddish in appearance. When the tumor has its seat in the cortex, it is often difficult to differentiate it from the surrounding tissue. Usually it can be differentiated from its surroundings by its color and consistency, and the presence of degeneration, which almost always occurs in it.

The consistency as well as the variations in appearance depend upon the age of the tumor, upon its vascularity, and upon the amount of retrograde change that it has undergone. The vascularity may be so great that the

tumor has all the naked-eye characteristics of a vascular tumor, and to these uncommon forms the name *glioma telangiectodes* has been given. Others show on cross-section foci of reddish softening which closely resemble hemorrhages, but on microscopic examination the lesion is shown to be not dependent upon rupture of any considerable vessel, but upon rapid disintegration of the tissues with exudation. The consistency of the tumor is usually greater than that of the tissue in which it is developed, unless retrograde and cystic transformation has gone on in it. In rare instances the glioma undergoes nearly complete cystic formation. A very uncommon mode of cyst formation which sometimes is seen in glioma is the formation of a cystic layer around the tumor-mass, and in such cases the degenerative changes go on most rapidly in the periphery. If in addition to such a degeneration there occurs an extravasation of blood into the center of the tumor-mass, it is often difficult to say whether any considerable gliosis has occurred or not. The histologic structure consists essentially in the formation of new glia-tissue, which has its beginning generally from the gray matter, although it may develop from and be limited to the white matter. In the oblongata and the cord it is probable that the original starting-point is around the central canal. On examination with low magnification the new growth reveals itself principally by the immense number of nuclei that are to be seen. When the tissue is examined with high-power lenses, it is seen that these apparent nuclei are really the crossing and juxtaposition of a number of fibers, the course of which can be traced to a considerable length. These filamentous processes radiate in every direction, and apparently without the least order. If these fibrillary radiations form a very close meshwork, as they often do, they produce a firm, compact tumor which has sometimes been called gliosarcoma, but careful examination of these cases shows that there is no cellular proliferation in the adventitial sheaths of the blood-vessel, and that the tumor is really made up of glia. The cells of the glia are of variable size: some of them are small and delicate and have a round or oval nucleus, while some are of large size and contain many nuclei. In some gliomatous tumors the cells that are found have a very striking resemblance to the ganglionic cells of the parts in which the tumor is developed, and the presence of these was thought at one time to indicate a hyperplasia of these cells (ganglionar neuroglioma). It is, however, generally believed that such a process never occurs. The nerve substance in which the tumor is developed undergoes less destruction than that which accompanies any other form of brain-tumor. The process of development of glioma is a peculiar infiltration. The new glia-tissue forms around ganglion-cells and axis-cylinders, and encroaches upon them in the beginning only to a very slight extent. After the new glia-tissue has developed somewhat, vascular changes occur, and these lead up directly to the disorganizing phenomena that go on in the tumor. The blood-vessels are abundant, many of them in a marked ectatic condition, with hyaline degeneration of their walls. Under the microscope it is seen that the tumor is not separated from the nerve-tissue by any sharp line of demarcation, such as is often seen on naked-eye examination, but that the former passes into the latter by gradual transition.

Gliomas occurring in the corpora quadrigemina, in the pons, and in the oblongata, as well as in the spinal cord, may usurp nearly the whole transverse area of one or more of these segments.

Sarcoma.—In adults sarcoma of the brain is more common than glioma, while in children the reverse is true. The tumor develops from connective tissue, its origin being from the connective-tissue cells of the pia and its prolongations, from the adventitial sheaths of the blood-vessels, or from the bone. The size of the sarcoma depends somewhat upon whether it is of primary or secondary development. The former are usually larger than the latter, and may be so great as to usurp nearly an entire hemisphere. Sarcomas that are limited by a capsule are usually smaller than the diffuse infiltrating variety. The former are hard and the latter soft. The color of brain-sarcoma depends, as does that of glioma, upon the amount of blood.

The histologic characters of brain-sarcoma do not differ from those of sarcoma in other parts of the body, and one sees here the same variation in size, shape, and contour of the cells as he does in sarcoma of other regions.

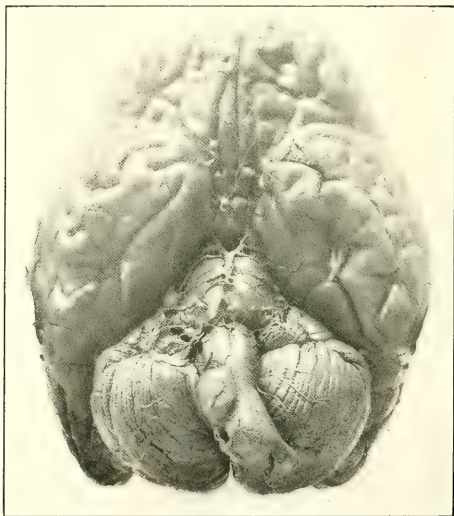


FIG. 202.—Sarcoma of the medulla oblongata (Riesman).

As a general rule, the connective-tissue development is very slight and insignificant compared with the round, spindle-, or stellate cells, but occasionally the former develops to a sufficient degree to make the term fibrosarcoma a warrantable one. Very exceptionally melanosarcoma occurs. When the sarcoma is rich in blood-vessels the tumor is often called angiosarcoma.

The changes that sarcoma produces in the brain-tissue in which it has its seat are not the same in every case. In the small, hard, white sarcoma which almost always occurs individually in the brain, there is scarcely any change in the surrounding tissue except that due to pressure. The tumor is surrounded by a fibrous sheath, which may assume the proportions of a capsule, and from this it can easily be shelled out, and examination of the cavity from which it was removed proves that there is no change in the

tissues except that of gradual disintegration; that is, there are no vascular changes or other indications of irritation. In the vascular form infiltration of the brain-tissue is often seen.

Tuberculoma.—The seat and frequency of these new formations have already been indicated. Tuberculomas may attain a considerable size, but are rarely larger than the closed hand; much more frequently they are of the size of a pigeon's egg. They form smooth, rounded, ovoid tumors, very sharply differentiated from their environment, and of a consistency dependent upon the amount of retrograde degeneration which they have undergone. They may be the seat of cysts, or their substance may be reduced to that of pulp. They are less frequently the seat of calcareous and other forms of degeneration than are sarcomas.

Gumma.—In point of frequency gumma is to the adult what tuberculoma is to the child. Like tuberculoma in another respect, it is not infrequently associated with formations of the same nature in other parts of the encephalon or other parts of the body. Although gumma is such a common form of neoplasm of the brain, it is not seen on the autopsy table with such frequency as glioma, for instance; and this is probably the consequence of the fact that it is the only form of intracranial growth that is amenable in any way to medicinal treatment. The gummatous deposit may be localized, and if so is very frequently in the cortex of the frontal and central regions. The tumor is not sharply differentiated from its environment, and on microscopic examination it is seen that there is a cellular infiltration dividing the characteristic grayish-red mass of round and spindle-cells from the normal area. The blood-vessels in the environment of the tumor are also degenerated, having the microscopic features of syphilitic endarteritis or of adventitial proliferation and subsequent thickening. Many of the vessels are completely occluded, while others show a lessening of caliber and marked leukocytal infiltration and exudation.

Carcinoma.—True cancers, using that term to signify an epithelial neoplasm, is a very rare intracranial disease. It is practically always a secondary growth. A few cases of so-called primary carcinoma of the brain have been recorded, chiefly of the choroid plexus, and of appendages of the brain, such as the pituitary gland. Secondary cancers of the brain usually occur in the form of small, round, multiple nodules, varying in size from that of a pea to that of a pigeon's egg, which encroach upon the brain and destroy everything with which they come in contact. The cortex, the brain-stem, and the hemispheres of the cerebellum are the most common sites.

Cholesteatoma.—A rare tumor is the neoplastic growth containing cholesterin, and made up of laminated layers of squamous cells. In exceptional instances it has been found to contain hair. Cholesteatoma is found oftener in the meninges than in the brain, but a few examples have been recorded as occurring within the brain substance.

Other forms of tumors, such as fibroma, psammoma, neuroma, osteoma, etc., have been described, but they are rare.

A few instances of lipoma have been recorded, and in these the ventricles and the appendages of the brain, such as the hypophysis and the corpora candicantia, were the usual seats.

Typical dermoid cysts have been recorded as occurring in the meninges and in the cerebellum in about half a dozen instances.

Parasites of the Brain.—The occurrence of parasites of the brain is very infrequent, especially in America. In Australia, in Southern and Central Europe, and in the polar regions it is not very uncommon. The principal parasites which invade the brain are the *Cysticercus cellulosæ* and the *echinococcus*. The cyst which the *Tænia echinococcus* produces varies in size from that of a walnut to that of an apple. Endogenous or exogenous daughter-cysts may develop, and thus add very materially to the size. Sometimes the little cysts take on a multilocular development.

These parasitic cysts develop slowly in different parts of the brain, and produce symptoms due to pressure and symptoms due to irritation or local inflammation. The local inflammation generally manifests itself by the formation of connective-tissue capsules. In some instances the cysts may cause pressure upon the bone sufficient to cause absorption of the latter and consequent protrusion of the cystic sac. See *Animal Parasites*, page 326.

DISEASES OF THE PERIPHERAL NERVES.

The peripheral nerves, unlike other parts of the nervous system, are devoid of bony protection, and are therefore more exposed to injury and injurious influences. The result is that they are often the seat of disease. Moreover, the peripheral nerves are prolongations of the cerebral nervous system, projected from or growing into the latter; hence, lesions of the peripheral nerves often accompany diseases of the central nervous organs.

Inflammations of the nerves have been divided, according to the constituents of the nerve first involved, into: (a) *parenchymatous neuritis*, when the nervous tissue proper is primarily or principally involved; and (b) *interstitial neuritis*, when the lesion is primarily of mesoblastic structures, the blood-vessels and supporting framework, the neural changes being secondary. This division is somewhat artificial.

Another classification of neuritis is one based on its etiology. Neuritis may be (1) traumatic, (2) toxic, (3) infectious, or (4) cachectic in origin. Under the second are included exogenous substances, such as alcohol, lead, arsenic, mercury, zinc, copper, phosphorus, and carbonic oxid; and substances of endogenous origin that have an injurious action on the peripheral nerves when carried to the nerves through the lymph and blood. This includes most of the cases of multiple neuritis that follow infectious fevers, such as diphtheria, typhoid fever, scarlet fever, septicemia, parotitis, endocarditis, malaria, tuberculosis, and occasionally beriberi. Under the third are included those cases of neuritis that are due to a specific infectious agency acting primarily on the nerve-trunks, such as the bacillus of leprosy and the specific cause of beriberi. It is possible that the bacillus of tuberculosis and that of syphilis may also act in this way. Under the fourth heading is placed neuritis occurring with or attributable to the various cachectic conditions, such as diabetes, rheumatism, gout, cancer, arteriosclerosis, etc. This form is probably due to toxic substances, of metabolic or extrinsic origin, circulating in the blood.

The peripheral nerves are formed by nerve-fibers collected into bundles by sheaths of connective tissue. Each nerve-fiber is made up of an (1) axone, (2) a medullary sheath, and (3) the sheath of Schwann, the primitive sheath, or neurilemma. The axone is the essential part of the nerve-fiber. A nerve-fiber is the prolongation of a neuraxone arising from a neurocyte.

The axones are longitudinally striated, due to the fine filaments or fibrillæ of which they are constituted. The fibrillæ often show small varicosities.

The myelin or medullary sheath is of a whitish color and composed chemically in great part of fat and water. It is of variable thickness, contributing more to the size of the fiber than any other constituent of the fiber. It is interrupted by constrictions or nodes, known as the nodes of Ranvier, which divide the nerve into a series of segments known as internodes. This segmentation is not apparent in the fresh nerve, but is strikingly shown after treatment with a solution of osmic acid, the medullary sheaths then staining black, the nodes remaining colorless.

The neurilemma or sheath of Schwann is a delicate membrane with prominent nuclei, one to each internode; it is continued over the nodes, although in passing over them it is constricted by a band of fibers, the constricting band of Ranvier. The tough sheath of Schwann is probably largely protective in its action.

The nerve-fibers are arranged in little bundles wrapped in a sheath of connective tissue, and these bundles are called funiculi. A number of the funiculi, also surrounded with connective tissue, constitute a peripheral nerve. The connective-tissue sheath around the nerve is called the epineurium, that around the funiculi is called the perineurium, while that between the nerve-fibers is called the endoneurium. The connective sheaths support the nerves and furnish a framework in which blood-vessels and lymph-vessels run. The blood-vessels of nerves divide into small branches in the epineurium, which pierce the perineurium and pass into the interior of each funiculus along the connective-tissue septa, and the capillaries are distributed around the nerve-fibers. The lymphatic vessels apparently do not continue as such beyond the epineurium; the epineurium contains lymph-spaces.

The changes in the peripheral nerves after injury vary with the severity and degree of destruction. If the continuity of a nerve is severed, the secondary degeneration occurs through the entire peripheral part, and in the proximal to the point of division as far as the first or second node of Ranvier. The myelin breaks up into balls and droplets and the axones disintegrate; the motor end-plates and even the muscles supplied by the nerve affected degenerate.

In addition to the Wallerian degeneration, definite changes occur in the cell-bodies of the corresponding neurones, consisting in a modification of the structure of the protoplasm, which reacts differently than the normal substance to methylene-blue. The nuclei of Schwann's sheath undergo karyokinetic proliferation. To this change in the cell-body the name of retrograde degeneration has been given. No portion of a neurone can be injured without in some degree affecting the entire cell. The real reparative process starts from the central stump of the severed nerve, from which emerge downgrowing axones. Complete restitution may occur. Vanlair has shown that the average speed of growth of new nerve-fibers is about one millimeter a day. The rapidity depends upon the conditions that the newgrowing axone has to overcome. If the territory through which it passes interposes no obstacles, and particularly if the remains of the old nerve are there to act as a sort of framework, then its growth is facilitated. But while the downgrowth of the new nerve-fibers takes place in the direction of least resistance, it is not solely under the influence of mechanic factors. Forssman.

has shown that the nerve-fibers of the peripheral end exert an attractive and guiding influence upon the new fibrils—an influence that is expressed in the term *neurotropism*. Not only the peripheral end of the same nerve, but the cut end of any nerve with which the central end may be brought into relation, exercises the same attractive influence. Even extracts of nervous tissue seem to possess it, while extracts of other organs have no neurotrophic power.

Neuritis.—Inflammation of single nerves, such as of the facial or the sciatic, are due to local causes, such as cold, injury, and extension of inflammation; constitutional conditions may predispose to neuritis. The inflammation is primarily of the connective tissue—so-called interstitial neuritis—the nerve-tissue being affected secondarily by the exudation and infiltration in the interstitial tissue.

Infectious forms of neuritis have certain pathologic features in common. The course of these forms is usually rapid. The changes in the nerves are not constant, but the parenchyma of the nerves is generally primarily involved. Hence, naked-eye changes may be scarcely noticeable. This variety of neuritis is usually known as parenchymatous. Microscopic examination may reveal all degrees of destruction, from simple swelling of the medullary substance associated with a beaded, swollen condition of the axones to complete destruction of the nerves, leaving an empty sheath of Schwann studded with newly formed nuclei. Many of the cells are loaded with myelin-detritus. If the process has been a slow one and of long duration, degenerative changes are found in the vasa nervorum.

Some of the infectious diseases act chiefly through the agency of toxins; among these are diphtheria, alcohol, and the disease known as beriberi.

In the terminal and convalescent stages of *diphtheria* variable changes occur in the nervous system. The processes in the nerves are interstitial and parenchymatous; the changes of the connective tissue predominate, however, and are in all probability the primary and the more important ones. The lesions are symmetrically distributed, the nerves of the throat and of the extremities being usually affected. The entire nerve-bundle is swollen, soft, and excessively vascular. Microscopically the nerve-sheaths, the blood-vessels, and the lymph-spaces of the nerves are the seat of inflammatory changes, the nerve-fiber undergoing degeneration.

A slight parenchymatous and interstitial anterior poliomyelitis may accompany this form of neuritis, the striking change in the ganglion-cells being a variable degree of vacuolation.

Alcoholic neuritis is characterized by the symmetry of its distribution and by its subacute course. In this form of neuritis there can be no doubt that the parenchyma of the nerves is primarily diseased; the interstitial changes are comparatively insignificant, and are probably secondary to the parenchymatous changes. In alcoholic neuritis the axis-cylinder is affected early and there are striking secondary changes in the muscles, a slight degree of myositis, characterized principally by an increase of muscle-nuclei, diminished distinctness of transverse structure, a tendency to the formation of connective tissue, and later fatty degeneration. Very rarely are pathologic changes found in the spinal cord.

Beriberi is an infectious or toxic disease, the most prominent lesion of which is a peripheral neuritis. Almost any nerve of the body may be affected, but those of the lower limbs are especially prone to involvement.

The pneumogastric, the phrenic, and the vasomotor nerves of the face are not infrequently the seat of the disease. The changes in the nerves are those typical of parenchymatous neuritis, although at times the lesion may be hemorrhagic. The blood-vessels are always the seat of well-marked changes. The most constant lesion is in the muscles. The muscle-fibers, when examined in the fresh state, are diminished in size, homogeneous or nearly so, having a colloid appearance. After hardening, the muscle-fibers show proliferation of the nuclei and decided proliferation of interstitial tissue.

Neuritis due to *mineral poisons*, such as lead, arsenic, mercury, zinc, copper, phosphorus, and carbonic oxid, is, in the beginning at least, characterized by segmental involvement of the nerves, the process being a typical peri-axial one of individual fibers. The axones remain for a long time intact. Later the medullary sheath is involved. It breaks it up into fine granules, and then some disintegration of the axones often occurs. Neuritis produced experimentally by the administration of lead is characterized particularly by the persistence of the axones and the degeneration of the medullary sheaths. The latter degenerate over short lengths of the fiber

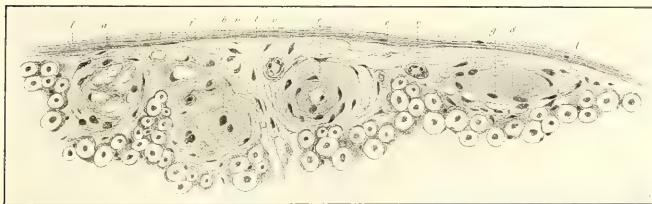


FIG. 203.—Large composite focus belonging to the mesoneurotic type and occupying the middle region of a spindle: *a*, an alveolar system; *b*, a group of elementary foci with nuclear elements as central corpuscles; *c*, a vacuolated nodule; *d*, the central mass is formed by a vitreous body cut obliquely; *e*, stroma interfasciculari with marked nuclei; *f*, diffuse form of mesoneurial tissue; *g*, condensed cells forming rudimentary nodules; *v, v, v*, blood-vessels.

corresponding to one or more internodes of Ranvier, between which the nerve-fiber remains normal. This form of neuritis is always accompanied with changes in the ganglion-cells of the anterior horns. It is, as yet, impossible to say whether the changes in the nerves or those in the ganglion-cells of the ventral horns are primary.

The neuritis that develops from the continued absorption of arsenic has nothing especially characteristic about it. For a long time it was disputed whether the neural lesions of arsenic poisoning were in the spinal cord or in the peripheral nerves. The truth is that they are not confined to either. The neuritis which arsenic produces is characterized by a thickening of the connective-tissue septa of the nerves, due to round-cell proliferation, by a thinning of the medullary substance and in some cases by its disappearance, which gives an appearance of relative thickening of the axone; leukocytic migration takes place. The lesions of the spinal cord are principally situated in the anterior horns, and consist of a progressive degeneration of the neurocytes, which are often markedly vacuolated.

In the forms of multiple neuritis accompanying cachexia the lesion is predominantly that of parenchymatous degeneration. Very frequently there are no evidences of inflammation whatever. When the nerves are

examined with the naked eye they are seen to be smaller than usual, and this is corroborated by the microscopic examination, which shows in many instances no other change than empty sheaths of Schwann. Occasionally there is found proliferation of the connective tissue and vessels with thickened walls, and in some cases with obliterated lumens.

The neuritis that occurs in diabetes may be looked upon as cachectic or toxic. In every case of this kind carefully examined microscopically profound changes in the large and small blood-vessels—sclerosis—have been discovered, and they may be responsible for the nerve-changes. The latter are by no means confined to the peripheral nerves, for striking alterations, such as atrophy of the ganglion-cells of the anterior horns and degenerative changes in the posterior columns, are also found. The degeneration begins by a splitting up of the myelin into short segments. The lesion of the peripheral nerves is predominantly a parenchymatous one, the destruction being confined almost entirely to the myelin-sheath; in some cases only a comparatively few nerve-fibers in a funiculus undergo destruction. The axones of the degenerated fibers, save for a somewhat beaded and varicose appearance, seem quite well preserved. With the parenchymatous changes there is always a slight increase of connective tissue, particularly manifest in the endoneurium and perineurium, but there is not any secondary degeneration. Associated with the neural changes, Fraser and Bruce have recently described a remarkable degeneration in the muscle-fibers, a disseminated interfibrillary, fatty degeneration of the muscle. It is characterized by a slightly increased distinction of longitudinal striation, which is due to rows of fine fat-granules between the fibrillæ and the muscle. These granules are all extremely minute, and seem to be developed from the cement substance and not from the muscle-fiber. Transverse striation of the fiber is lessened.

The neuritis of syphilis and that secondary to disease of the blood-vessels have much in common. Syphilitic neuritis is most frequently observed in some of the cranial nerves secondarily to a basal meningitis. In such cases the neuritis is practically a simple degeneration. In other cases the granulation-tissue characteristic of syphilis extends into the substance of the nerves, developing in the connective-tissue septa, and causing secondary degenerative changes by virtue of their presence. In almost all cases of this kind endarteritis is present.

The neuritis associated with disease of the blood-vessels is practically a senile change and of a degenerative nature. The changes are principally in the connective tissue of the nerves and in the blood-vessels. The disease of the vessels is particularly marked in the arteries, but it occurs also in the veins; it consists of a thickening of the walls, not only of the adventitia, but of the media and the intima as well. Accompanying these there is a narrowing of the lumen of the vessels, and thrombosis often occurs. Accompanying this there are proliferation also of the endoneural supporting tissue, and a more or less complete shrivelling of the nerve-bundles. In almost every case of this kind reported there seems to have been a sort of ascending degeneration, extending up as far as the ganglion-cells of the anterior horn, and a degeneration of the posterior roots, with consecutive ascending degeneration in the posterior columns. This, in connection with the fact that with profound involvement of the blood-vessels there are always degenerative and inflammatory changes in the muscles, leads to the con-

clusion that in such instances the changes in the peripheral nerves are but a small part of the universal degeneration which has resulted through disease of the vascular system.

Two other forms of neuritis need special mention, viz., tuberculous neuritis and leprous neuritis. These two forms of neuritis, although both due to a specific organism, are quite different in their morbid anatomy. Tuberculous neuritis is a typical parenchymatous degeneration, while the neuritis of leprosy is typically interstitial, the lesion being confined almost exclusively, at least in the earlier period of the disease, to the connective-tissue sheath of the nerve. It causes an increase of the connective tissue of these parts, and in the cellular proliferations the lepra bacilli are found in great abundance. The changes in the nerves proper in leprous neuritis are secondary and degenerative; this accounts for the clinical picture of anesthetic leprosy. Neuritis in tuberculosis may or may not be attended with clinical symptoms. The neuritic process itself may develop very quickly or it may occur in a latent form.

THE OSSEOUS SYSTEM.

THE BONES.

INTRODUCTORY.

Bone-tissue and Medullary Tissue.—Externally bone is covered with periosteum, which consists of an external fibrous layer and an internal layer of cubical cells, the osteoblasts.

Bone-tissue proper consists of oblong, flat cells, with numerous processes embedded in a calcified, densely lamellated ground substance. Bones are composed of an external compact layer and an internal cancellous or spongy substance. In the spaces of the spongy tissue lies the bone-marrow or medullary tissue, which communicates with the periosteum and parosteal tissue by the Haversian and Volkmann's (or perforating) canals, which perforate the compact layer and carry blood-vessels, lymphatics, and nerves. Around the Haversian canals the bone-tissue is arranged in concentric lamellæ closely apposed, while in the cancellous layers it is arranged in the form of a trabeculated network enclosing the medullary spaces.

The marrow varies in structure and appearance according to the age and to the bone. There are recognized the red or lymphoid marrow and the yellow or fatty marrow.

The red or lymphoid marrow is found in all bones in children, and in the short and flat bones of the grown. It is soft, red, rich in cells and in blood-vessels. The supporting tissue consists of branching cells forming a fine network, in which are suspended the wide, delicate, and thin-walled vessels in such a manner that collapse is impossible. A large variety of cells are present: as myelocytes, lymphocytes, multinuclear giant cells (myeloplaxes), nucleated red blood-corpuscles, hematoblasts, eosinophilous cells, and red blood-corpuscles.

The red or lymphoid marrow is most richly cellular in early years; with time the number of cells diminishes, especially in the long bones, the supporting connective-tissue cells change into fat-cells, and, after the fourteenth to the sixteenth year, the long bones of the extremities contain fatty or yellow marrow. The lymphoid marrow persists in the short and flat bones. When the fatty marrow is more or less anemic, it is yellow; when congested, yellowish red in color.

The functions of the bone-marrow are various. It is a hematopoietic organ, and is closely allied, histologically and functionally, to lymphadenoid tissue. It contains multinucleated giant cells, that act as osteoclasts and absorb bone. Bone-marrow is one of the places in the body in which foreign substances in the blood are retained and undergo further changes that may render them harmless.

The Relation of the Marrow to General Diseases.—The marrow may present a number of changes that are more or less independent

of the diseases of the bones proper. These changes are in part primary and noninflammatory and include the diseases of the marrow as a blood-forming and lymphadenoid tissue, and in part secondary to various general infectious and exhausting diseases.

The changes in the marrow in the various forms of leukemia and pernicious and secondary anemias are described elsewhere.

In senile marasmus and in chronic pulmonary tuberculosis, chronic nephritis, and like diseases, the marrow may undergo atrophy and degeneration, serous fluid taking the place of the fat, giving the marrow a mucoid or gelatinous appearance—the gelatinous marrow. At times lymphoid marrow develops in place of the fatty. In many infectious diseases fatty changes take place in the capillaries and arterioles and in the medullary cells. Focal necroses may occur. In infectious diseases the fatty marrow not infrequently changes by metaplasia back to the lymphoid; the change commences near the epiphyses and spreads into the shafts. The number of pigment-cells and cells containing red blood-corpuscles is increased.

In malaria the amount of pigment in the marrow-cells is increased, and lymphoid substitution of the fatty marrow is noticed.

The tendency of the marrow to retain foreign substances undoubtedly plays an important part in the genesis of the suppurative, tuberculous, and other forms of osteomyelitis; microbes may be recovered from the bone-marrow after infectious diseases, and, in the case of typhoid fever, the bacillus may remain latent in the tissues for a long time.

Embolism of marrow-cells, especially the multinuclear, is probably of frequent occurrence (Lubarsch). It seems almost constant in puerperal eclampsia and in infectious diseases; it takes place also in concussion of bones and in fat-embolism, even though the fat is not derived from the marrow; and Lengemann has shown that every form of experimental cell-embolism gives rise to a secondary embolism of the giant cells in the marrow.

Normal Osteogenesis.—Bones arise partly in a connective-tissue matrix (intramembranous ossification), partly in a cartilaginous (endochondral ossification).

A growing long bone presents the following features upon the cut surface: the shaft is completely ossified; in the cartilaginous epiphyses are independent points of ossification; and at the junction of the diaphysis and the epiphysis is the intermediate cartilage, in which the naked eye usually recognizes two zones—a bluish, transparent layer (the zone of proliferation), and, between this and the limit of the bone, a yellowish-white, narrow, linear seam (the zone of calcification).

In the zone of proliferation the distal part corresponds microscopically to the layer of actively multiplying cartilage-cells; the cells divide by mitosis, and often one capsule contains two or more cells. It is here that the growth of the bone in length is provided for. Then follows a district in which the cartilage-cells are arranged in columns, and in the upper part of this area the cells are very large. Now comes the zone of calcification—the straight, yellowish-white line visible to the naked eye, immediately adjacent to the apparently ready bone. Microscopically the zone of calcification is succeeded by a layer of medullary spaces, from which the adjacent cartilage is absorbed. In this manner the cartilage gradually becomes replaced by bone. The bone in the epiphyseal center continues to grow in all

directions, and, when fusion of the epiphyseal and diaphyseal bone occurs, the growth of the bone in length ceases; this occurs normally between the twentieth and twenty-seventh years. The articular cartilage is permanent and does not produce much bone. If the epiphysis, together with the intermediate cartilage, is removed during the period of development, then the growth in length ceases.

Absorption and New Formation of Bone.—Bone is not the unchangeable, permanent structure that its hardness and firmness would indicate; it is the seat of constant reconstruction during the entire lifetime, and, under pathologic conditions, the resorption of existing and the formation of new bone are frequent processes.¹

"The architecture of bone is subservient to function. It is not to be so understood that the internal arrangement of the septa and trabeculæ in the bones is a matter of chance. The architecture and form of bone are influenced by two functions: static, *i. e.*, the lines along which pressure is exerted; and mechanic, *i. e.*, the directions in which muscles pull." When the static conditions of the femur are altered, its whole internal structure changes. After each fracture there is, in addition to the callus production, a rearrangement of the septa in the fragments, both distal and proximal. A similar rearrangement occurs under all conditions that change the static and mechanic relations of any bone.

Absorption of bone occurs most frequently in the form of *lacunar resorption*. There arise oval and irregular depressions upon the surface of the bone and the bone-trabeculæ, in which lie smaller and larger multinucleated cells, the osteoclasts of Kölliker (also called myeloplaxes), which remove the bone *in toto* without any preliminary decalcification. The resulting depressions are known as Howship's lacunæ. Lacunar resorption gives the surface of the bone a rough appearance, as though an animal had gnawed upon it.

Bone may be removed without osteoclasts; decalcification takes place, and the ground substance of the bone appears as osteoid tissue. Subsequently the osteoid tissue is dissolved or incorporated in the medullary tissue, becoming first somewhat more fibrillated than normal. This process is called *halisteresis*, and occurs mostly under pathologic conditions. Halisteresis is often marked by the appearance of variously shaped lines and markings in the bone, which depend upon the resorption of the lime salts in the inter-fibrillar spaces. These figures are rendered distinct by the injection into the bone of air or carbonic acid; they are then seen in the still calcified bone, near the margin of the decalcified zone (von Recklinghausen's "Gitter-figuren").

Bone is also resorbed by the so-called *perforating canals*. Physiologically bone contains canals, inclosing vessels, which pass between the Haversian canals, but are not surrounded by concentric lamellæ. Under pathologic conditions, vascular connective tissue makes its way through the intervening lamellæ from one Haversian space or canal to another. According to Pommer,² these canals are in part produced by vascular sprouts; the cavities containing bone-cells may become irregularly dilated, and, by the confluence of several cavities, perforating passages are produced, and, upon opening a medullary space, they become filled with cells.

¹ Wolff, *Das Gesetz der Transformation der Knochen*, 1892.

² *Osteomalacia u. Rachitis*, 1885.

The formation of new bone occurs according to the same principles in pathologic and physiologic conditions. The tissues that can form new bone are the periosteum, the bone-marrow, the cartilage, and, to a limited extent, the connective tissue. Of these, the most important are the periosteum and the marrow. In the periosteum it is the inner layer—the cambium of Billroth, or the proliferating layer of Virchow—that has osteoplastic power; this layer is connected by means of medullary canals and spaces with the marrow, in which are similar osteoblasts.

The formative cells are produced by mitosis from the pre-existing cells in the periosteum and the marrow. The osteoblasts produce a homogeneous or finely fibrillated ground substance which becomes lamellated bone by impregnation with lime salts, while the osteoblasts are buried as bone-cells in small cavities provided with numerous projections; or the cells first produce cartilage, which is subsequently replaced by bone.

When new bone is deposited directly upon existing bone-lamellæ, growth occurs by apposition, and this is the only way fully developed bone grows; expansive growth by the insertion of new elements does not occur.

New bone is formed also by metaplasia from fibrous connective tissue and cartilage.

DISTURBANCES IN THE GROWTH AND DEVELOPMENT OF BONE.

Defects.—Failure of development of a bone or portion thereof may be due to an original absence of the anlage (aplasia), or the part may have been destroyed or hindered from further development during intra-uterine life.

The skull may be absent, as in acephalus; or it may be defective, as in anencephalus, cyclops, and various other monsters. The spinal column may be rudimentary, as is the case in a number of malformations, such as iniencephalus and spina bifida. Occasionally one or more vertebræ may be absent. There may be clefts in the thorax, as in thoracoschisis; and arrest of growth in the costal cartilages may lead to the malformation known as funnel-shaped thorax. Parts or the whole of bones of the extremities may fail to develop.

Hypoplasia.—Hypoplasia, or arrest of development, of the skeleton may begin in intra-uterine life, or it may appear during the postnatal period of growth. It may be general and uniform or limited to single bones.

Congenital hypoplasia of the skeleton is characterized by shortness of the extremities, and the soft parts, being normally developed, are too wide and too long for the limbs; consequently the skin may lie in extensive folds, like a garment that is too large.

Congenital conditions like these have been known by a number of terms, such as microsomia, manosomia, micromyelia, fetal rickets, micromyelia chondromalacia (Marchand), chondrodystrophia foetalis (Kaufmann¹); but upon the basis of recent investigations, especially by Kaufmann,² Hildebrandt³ divides the fetal bone diseases which enter into consideration in connection with this subject into (1) genuine rickets, (2) chondrodystrophia foetalis, (3) syphilitic bone disease, and (4) osteogenesis imperfecta. Just now we are interested especially in chondrodystrophia foetalis.

¹ *Die sogenannte foetale Rachitis*, Berlin, 1892.

² See also Johannessen, *Ziegler's Beiträge*, xxiii., 351, 1898.

³ *Virchow's Archiv*, clviii., 426, 1899.

In this as well as in other instances of arrested ossification the anatomic cause is insufficient proliferation of the cells in the epiphyseal cartilages and premature arrest of endochondral ossification. In a number of cases marked changes have been found in the epiphyseal cartilages (Marchand, Kaufmann); the cartilage-cells may fail to multiply, and the zone of proliferation is practically absent; the cartilage may undergo softening; the proliferation may occur in an erratic, extravagant manner, so that the epiphyses are broad and large, but the diaphyses are short (Fig. 204). In the last case it also happens (Kaufmann) that a layer of connective tissue is interposed between the shaft and diaphysis, resulting either in complete arrest in length or in curvatures. The base of the skull may become shortened by the premature arrest of cartilaginous proliferation, *i. e.*, premature synostosis of the sphenobasilar and intersphenoid synchondroses. This gives rise to the depression of the root of the nose, which is often characteristic of these individuals.

In the case of osteogenesis imperfecta described by Hildebrandt the

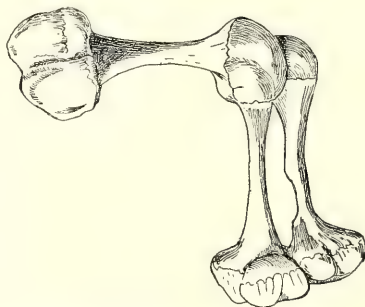


FIG. 204.—Chondrodystrophia foetalis (after Kaufmann).

fault did not seem to rest so much in the changes in the cartilage as in an imperfect ossification.

In the extra-uterine arrest of growth in length the soft parts may be developed in excess of the extremities, or there may be a proportionate hypoplasia of the soft tissues as well as of the skeleton. Many dwarfs are otherwise normal individuals. According to Kundrat, the process of ossification may be of a normal type, but quantitatively insufficient.

Among the examples of postembryonal arrest, the cretins and cretinoid individuals are characterized by short, blunt bones, broad face, a depressed insertion of the nose, low forehead, and functional as well as often morphologic cerebral abnormalities. Many have goiters, others atrophic thyroids; the skull is the seat of a premature synostosis of the sphenobasilar synchondroses (Virchow); myxedema may be present.

In many of the cases alluded to the cause of arrest of growth cannot be determined. In the cretins and cretinoid individuals, however, it is quite definitely settled that the condition depends upon the absence or the disturbance of the functions of the thyroid gland. Quite similar changes in

the cartilages as occur in chondrodystrophia foetalis have been produced by experimental thyroidectomy in young rabbits (Hofmeister¹).

Individuals affected with chondrodystrophia usually die in the first few weeks after birth, but some have lived for twenty or more years; and in these it has been observed that the mental development was fairly good, so that it is evident that other conditions than absence of the thyroid function may produce the disease. Congenital rickets, which is usually made responsible for the arrest of growth, is surely not so frequently the cause as has been thought, because the anatomic lesions above outlined are not those of rickets; but the occurrence of congenital rickets cannot be denied. In



FIG. 205.—Hyperostosis of the femurs associated with long-continued passive congestion.

other cases the cause must be looked for in developmental anomalies of the central nervous system (microcephaly, hydrocephaly, anencephaly), and often the condition is associated with idiocy due to other causes than cretinism. Postnatal rickets and other diseases may also lead to arrest of growth.

Excessive Growth.—Excessive or giant growth may be general or partial. The cause of general giant growth is not known. The bones of giants are often disproportionate, excessively fragile, or covered with exostoses. The nature of the relation thought by many to exist between giantism and acromegaly has not yet been made clear.

¹ *Beiträge von Bruns*, xi., 1894.

Partial giant growth may involve the fingers, toes, the cranial or facial part of the head. The enlargement of long bones may depend, on the one hand, on increased endochondral ossification, which leads to excessive growth in length, or to excessive growth by apposition, which would result in increase in thickness. The cause of the partial giant growth, as well as of many closely related exostoses and other hyperplasias, is not known.

Increased growth in length in the young—elongation—often accompanied with hyperostosis and due to acquired causes, may depend upon various diseases and injuries of the diaphysis, such as osteomyelitis and fractures; upon diseases of the soft parts, such as ulcers, suppuration, dilated veins; and upon tuberculosis and other diseases of the neighboring joints. In these cases the elongation, which may reach several centimeters, must depend upon a continuous stimulation of the epiphyseal cartilage, the cells of which proliferate more rapidly, while the hyperostosis is due to proliferation of the periosteum.

Experimentally it has been shown that, by driving ivory pegs into the cartilage of young animals, an abnormal elongation may result. It is generally believed that hyperemia of bones is conducive to growth by apposition.

Premature Synostosis.—The premature synostosis of a suture, or of a synchondrosis, arrests permanently all further growth at the point involved.

In the pelvis, premature synostosis of the sacro-iliac synchondroses causes a uniform contraction of the pelvis; if on one side only, the obliquely contracted pelvis.

Premature synostosis of the cranial sutures arrests the further growth of the cranium vertical to the synostotic suture; in case only one suture is closed, the brain causes compensatory expansion of the cranium in other directions. Premature synostosis of the intersphenoid and sphenobasilar synchondroses leads to shortness of the cranial base and causes a deeply inserted nose. In microcephaly there may or may not be premature synostosis of all or of the majority of the sutures. The exact relation of microcephaly to microencephaly as regards cause and effect has not been made out, but in many cases the latter condition is the primary.

CIRCULATORY DISTURBANCES.

Growing bone is the seat of a physiologic hyperemia of the periosteum and of the medullary tissue near the centers of ossification.

Passive hyperemia of bones develops when there is obstruction to the current in the veins that drain their interior, as would be the case in general venous obstruction, and, in the bones of the skull, in extensive thrombosis of the sinuses of the dura. A hyperemic bone shows a reddened periosteum, the substance of which is somewhat swollen; the lymphoid marrow becomes deep red, and the fatty marrow yellowish red.

Simple passive hyperemia causes the clubbed finger-ends seen in chronic pulmonary and cardiac diseases. Hyperostosis is sometimes observed after long-continued passive congestion and edema, and it would seem as though venous hyperemia in some manner induces the formation of bone.

Hemorrhage occurs in consequence of wounds of the periosteum, the bone, and the marrow; but it is not of any essential importance, the extravasation being rapidly absorbed. Hemorrhage may also result from destructive

processes in the interior of the bones, but does not reach any extent except in the interior of tumors, especially of sarcoma, where large blood-cysts may form. In purpura, hemorrhagic diathesis, including Barlow's disease, and scurvy, punctiform extravasations occur under the periosteum and in the marrow. The so-called cephalhematomas of the newborn are subperiosteal extravasations, usually situated upon the parietal bones; they develop on account of tearing of the periosteal vessels in the course of difficult labors, and do not, as a rule, extend beyond the sutures at which the periosteum is closely adherent to the bone. Occasionally there may be an internal cephalhematoma, situated between the bone and the dura. Usually the blood is absorbed, while a bony elevation may be formed at the circumference of the hemorrhage.

In the so-called infantile scurvy (Barlow's disease), interesting changes take place in the bones. In this disease there is a marked tendency, of unknown cause, to multiple hemorrhages, and numerous subperiosteal and endosteal hemorrhages take place, especially at the points of physiologic congestion and active growth, such as the inner layer of the periosteum and the lines and areas of ossification. According to Jacobsthal,¹ the bone about the hemorrhages is absorbed, a new tissue with but few bone-trabeculae develops, and, while the cartilage-cells proliferate freely but atypically, the cartilage is not replaced by bone. This disturbance of endochondral ossification leads to an abnormal fragility at the osteochondral junctions, and the epiphyses separate easily.

Thrombosis of the vessels of bones occurs, after injuries and solutions of continuity, in the vicinity of acute necrotic processes and of hemorrhages; circulatory disturbances do not result from thrombosis of single osseous veins, because of the abundant anastomoses.

Embolism of the arteries of bones is currently regarded as without mechanic effect on account of abundant anastomoses. Gussenbauer found in the ends of diaphyses circumscribed areas of capillary networks which were supplied by only one artery; this would correspond to an end-artery in Cohnheim's sense. The so-called tuberculous infarcts in the epiphyses also point to the existence of end-arteries, the embolic closure of which may cause anemic necrosis of pyramid-shaped areas (Fig. 206).

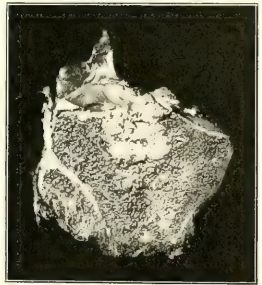


FIG. 206.—Tuberculous embolic infarct in the head of the tibia, perforating into the knee-joint.

RETROGRESSIVE CHANGES.

Simple Atrophy.—By simple atrophy of bone is meant the gradual disappearance of bony substance by the way of increased lacunar, normal resorption. Disintegration of bone due to inflammatory processes is known as caries. When bone is deprived of its lime salts, so that it becomes soft, the condition is known as osteomalacia.

Atrophy by lacunar absorption may take place upon the surface of the bone. The osteoclasts produce large and numerous Howship's lacunæ, so

¹ Ziegler's *Beiträge*, xxvii., 172, 1900.

that the surface becomes rough and irregular, while the bone becomes thinner and thinner, due to the gradual absorption of its substance—concentric atrophy. When excessive lacunar absorption occurs in the interior of the bone, so that the trabeculae become thinner and thinner and the medullary spaces larger, while the Haversian canals of the compact bone enlarge to form spaces, then the atrophy is spoken of as excentric or as osteoporotic (Fig. 207).

The process of absorption in atrophy of bone need not exceed the normal; there may be simply an arrest of the continuous growth by apposition, which occurs under normal conditions, and then the absorption becomes relatively excessive (Pommer). In other cases the absorption may become absolutely increased.

The medullary tissue of atrophic bone may be fatty; in excessive maras-



FIG. 207.—Atrophy of bone (osteoporosis) in the femur of an old man suffering from senile coxitis.

mus it may be infiltrated with serum, which takes the place of the disappearing fat (serous atrophy of fat-tissue). In some instances the medulla may be the seat of cellular hyperplasia and present itself as lymphoid marrow.

Atrophic bones are light and fragile; the saw passes through their substance without much resistance.

Excessive brittleness of bones is known as *fragilitas osseum* or *osteopsathyrosis*; it may occur as the result of the atrophy of senile and other forms of marasmus, in the so-called neurotic atrophy of *tabes dorsalis* and *syringomyelia*, as a result of prolonged inactivity, and in connection with rickets and osteomalacia. In occasional rare instances it appears in “idiopathic” form without known etiology and without any definite anatomic basis (Volkman¹); the condition may appear to be inherited.

Senile and marantic atrophy occurs in old age and in younger individuals

¹ *Handbuch der Chirurgie*, ii., 1872.

suffering from marasmus due to various chronic diseases; it may involve the entire skeleton in varying degrees. Generally speaking, the bones become fragile and fracture easily, while some bones become abnormally soft and are cut with ease; the latter condition is more of a senile or marantic osteomalacia. It is generally believed that anemia of bone favors absorption and hinders apposition, and it may be one of the factors in these forms of atrophy. The atrophy may be concentric or excentric. It begins, as a rule, at those points that are free from muscular attachments. In the calvaria the bone becomes thin, granular, and finely porous, especially in the temporal regions; as atrophy occurs in the external table, the internal may become rough from the production of new bone. In the maxillæ the alveolar processes may disappear completely. The flat bones may become extremely thin, and full of smaller and larger defects. The vertebræ may be either porous or become uniformly smaller, so that the spinal column becomes shorter. In the long bones osteoporosis is usually marked.

Atrophy of bone due to pressure is common; it is caused by the continuous pressure of various formations, such as aneurysms and tumors, located within, upon, or contiguous to, various parts of the skeleton; contracting cutaneous cicatrices; inflammatory and other products in unyielding bone-cavities, such as the middle ear, the antrum of Highmore; increased intracranial pressure due to hydrocephalus, tumors, or abscesses; the so-called pachionian granulations of the dura, etc. In consequence of pressure, there result more or less circumscribed defects, around which it is not unusual to find new bone produced by apposition.

Atrophy from inactivity results in the formation of thin and short bones. It is observed in its most typical form in consequence of inactivity during the period of growth, due, for instance, to infantile paralysis (neuroparalytic atrophy) or to joint and bone inflammations.

Atrophy of bone is observed in paralytic dementia, syringomyelia, and tabes dorsalis.

Necrosis.—Local death of bone occurs in osteomyelitis and periostitis on account of direct interruption of the circulation, due to the intensity of the inflammation. The further fate of the necrotic piece, or sequestrum, is described under Suppurative Osteomyelitis. Necrosis of bone may also result from chemical or thermal agencies; in comminuted fractures, the nutrition of single pieces being entirely suspended; necrosis probably also results from the occlusion of end-arteries in the epiphyseal extremities of long bones, as seen in the so-called tuberculous infarct; atrophic necrosis due to the involvement of the trigeminus nerve is described as occurring occasionally in the mandible in the course of tabes dorsalis (Kolischer); the so-called phosphorus necrosis is in reality an infectious periostitis and osteomyelitis. In all these cases the necrotic tissue, or sequestrum, becomes separated from the healthy tissue by a reactive inflammation associated with processes of rarefaction and absorption. If suppuration is present, which is usually the case, the absorption of the sequestrum may be greatly delayed.

Necrosis in bone conveys the idea of death of a large piece. Caries means a gradual disintegration of bone substance without any visible sequestrum; it is seen most frequently in connection with bone or joint tuberculosis. When the carious destruction is accompanied with the formation of palpable, sand-like granules of dead bone, molecular necrosis is said to occur.

Caries is always the result of inflammation of the soft tissues in the bone-spaces.

REGENERATION AND HYPERPLASIA OF BONE.

Hypertrophy and Hyperplasia.—New bone may form in the repair of solution of continuity, *e. g.*, fractures, traumatic and other defects. New bone is also formed under various other conditions.

Hyperplasia or hypertrophy of bone is nearly always a secondary process. Hypertrophy upon a congenital basis, the exact nature of which is not understood, occurs in connection with general and partial giant growth. A compensatory hypertrophy of bone occurs, and a classical example of this adaptive process is seen, in the great increase in the size and thickness of the fibula when the tibia is rendered functionless on account of ununited fracture and other conditions.

The formation of new bone is observed in a variety of diseases of bone and contiguous tissues, and it is constantly referred to in the discussion of inflammations and tumors of bone. It is often difficult, and sometimes impossible, to distinguish between many of these secondary hyperplasias, which persist long after the primary conditions subside, and the true osseous tumors that arise from the proliferation of osteoblastic tissue according to

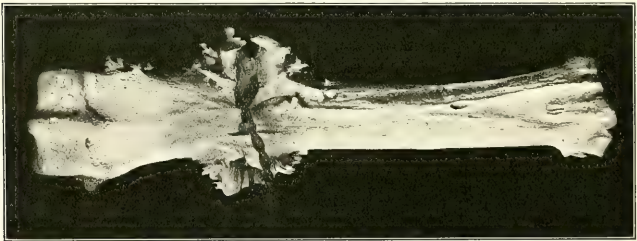


FIG. 208.—Abundant osteophytes about a piece of barbed wire which penetrated one of the metatarsal bones of a cow.

principles of tumor-growth. Hyperplasia of bone probably also occurs secondarily to passive congestion.

When a bone acquires a distinct increase in volume, due to the addition of new osseous tissue, it is spoken of as hyperostotic. When a bone acquires increased density due to the deposition of new bone upon the old trabeculae or to the formation of new osseous trabeculae in its interior, then condensation or osteosclerosis is said to have taken place. A sclerotic bone is increased in weight, but not necessarily hyperostotic. Hyperostosis may be either spongy or sclerotic. Circumscribed new formations of bone in the spongiosa are usually known as enostoses. Circumscribed nodular or flat periosteal inflammatory bone formations are called osteophytes (Fig. 208). Exostoses are circumscribed external new formations of bone that in their genesis correspond more closely to true tumors.

The Healing of Fractures.—When a bone breaks, either completely or incompletely, there results more or less hemorrhage; the surrounding tissues are torn and infiltrated with blood; a moderate degree of

inflammatory exudation and cellular emigration takes place, but in the absence of infection the inflammation subsides after a few days, to be followed by regenerative proliferation. As early as on the second day there are abundant karyokinetic figures in the cells of the periosteum, the medullary tissue, the adjacent fibrous tissue, and the vascular endothelium; and on the fourth and fifth days a vascular formative tissue has developed, which is rapidly differentiated into osteoid and chondroid tissue.

The formative tissue produced by the periosteum is known as the external callus, that which extends in between the fragments as intermediary callus, while the tissue from the medulla is known as the internal or myelogenic callus.

The periosteal or external callus extends around the fragments like a spindle-shaped capsule for some little distance on each side of the break. At the end of the first week the inner layers of the formative tissue, composing the periosteal callus, have become differentiated into osteoid tissue and hyaline cartilage (this is so especially in children and in some animals, like the rabbit and dog), which very rapidly change by calcification and metaplasia into new-formed porous bone—the bony callus. During the succeeding two or three weeks the amount of bony callus constantly increases.

The myelogenic callus is formed by the proliferation of the osteoblasts of the medulla; it is not of such importance as the periosteal callus, and consists of a small amount of formative tissue that projects for a little distance into the medullary canal on each side of the fracture.

When the fragments are widely separated, they are reunited by the formation of an extensive intermediary callus, which connects the myelogenic with the periosteal. It is produced essentially by the periosteum, but also to a certain extent by the marrow. The parosteal callus is the formative tissue produced by the adjacent connective tissue.

This callus, also called provisional, grows in amount until about the fourth or fifth week of the fracture (man); and at about the seventh week, it is totally ossified. It now consists of a porous, rather soft, osseous tissue, which gradually becomes substituted by new bone of considerable density by means of lacunar resorption and the formation of medullary spaces on the one hand, and the production of new lamellæ or growth by apposition on the part of osteoblasts on the other. In this way is produced a more solid, dense bone—the definitive callus. The definitive callus does not remain unchanged, however, but undergoes further reconstructive processes, composed of lacunar absorption and growth by apposition, that tend to produce the bony architecture best suited to the functional requirements. When great dislocation of the fragments or splintering has occurred, it may take months and years before the reconstructive and reparative processes are finally completed; the bone-mass is reduced, the projecting fragments are rounded off, and the weak points strengthened. The mass of external callus is reduced, the spindle-shaped or irregular swelling disappears by concentric atrophy, and the internal callus may, when the apposition of the ends is perfect, become absorbed so that the lumen of the medullary cavity is restored. In case of great dislocation the medullary canal is usually not re-established.

The size of the callus varies much, depending on the extent of the fracture and the dislocation of the fragments. Comminuted fractures with much dislocation are often followed by the production of a large amount of callus (Fig. 209).

Luxuriant callus is the excessive production of new bone, which may fail to become absorbed; circumscribed masses of luxuriant callus are known as osteoma fracturæ, and similar cartilaginous outgrowths as chondroma fracturæ (Fig. 210).

When neighboring bones—as, for instance, those of the forearm and leg—are broken, the resulting callus may produce synostosis. Fractures involving joints may be followed by extensive callus formation on part of the joint-structures, and ankylosis may result.

Fractures heal more rapidly in children than in old people, and, on an average, in two or three weeks. In old age and severe cachexia, healing may occur very slowly.



FIG. 209.—Great thickening of femur, following a compound comminuted fracture below the trochanter.

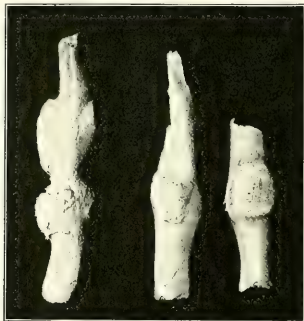


FIG. 210.—Callus-tumors in the ribs of a sheep.

Smaller bones unite earlier than the larger. Complicated fractures accompanied with periostitis and osteomyelitis may require a long time to heal; the formative tissue is destroyed by the infection, and the bone may undergo caries and necrosis.

Failure of bony union leads to the formation of a false joint or pseudoarthrosis. It results when the bone-forming power of the periosteum is suspended on account of extensive destruction, when the fragments are not suitably immobilized, too far removed from each other, or when muscular fibers or fascia come between the ends of the fracture. Severe cachexia and senility also lead to nonunion. The fragments may be more or less closely held together by bands of cicatricial tissue, or there may be an absence of all connection; the ends may be polished, they may even be covered with cartilage and surrounded by a more or less complete capsule (nearthrosis).

Bone Grafting.—The results obtained by grafting with living bone

vary according to different investigators. Macewen and Ollier believe that homoplastic grafts implanted in the long bones take, in the sense that the bone retains its vitality and helps directly to supply defects.

Barth¹ has studied the histologic changes in implantation of living bone into freshly made openings in the skull, and found that the grafts invariably die and are gradually substituted by new bone from the formative tissue produced by the dura and the medullary tissue of the diploe. Precisely the same results were obtained by the implantation of dead, macerated pieces of bone. Decalcified dead bone did not seem to become so readily replaced by new bone; it was more rapidly dissolved, and the defect was filled by connective tissue. For the purpose of healing large defects in bone, Tillmanns prefers sterile, fresh, small bone-particles of man or animals, with periosteum and medulla, preferably from growing bones. The presence of lime salts in the implanted bone seems, therefore, to be of some importance. Senn and other investigators report good results with decalcified chips. Periosteal grafts are generally regarded as capable of producing new bone (Ollier).

INFLAMMATIONS OF BONE.

Introduction.—Inflammatory processes in bone are divisible into two groups, namely, periostitis and osteomyelitis. It is to be noted that osteitis is in reality an osteomyelitis, because it is an inflammation of the tissues situated in the medullary spaces and vascular canals of the bones, associated with secondary changes in the surrounding bone substance.

Inflammations of bones are generally associated with osteoplastic processes that must be looked upon as in part of a regenerative nature, furnishing tissue for the repair of defects produced by the inflammatory caries and necrosis, but also in many cases as due to the stimulation of the osteogenetic tissues by the inflammatory agent.

Inflammation of the bone may be due to local causes or to agents in the blood. In either case the agents may be of infectious or noninfectious nature, but the importance of the infectious inflammations is manifold greater than the noninfectious. Hematogenous inflammations may be metastatic or primary.

Periostitis.—Fibrous Periostitis.—In this form of inflammation the periosteum involved becomes changed into a dense, hard mass of scar-tissue, which is firmly adherent to the underlying bone. The process arises in consequence of persistent "irritation" of the periosteum in the neighborhood of chronic necrotic and inflammatory lesions in the interior of the bone, of chronic joint-lesions, of chronic inflammation and ulceration in the adjacent soft parts (ulcer of the leg, elephantiasis), and also as the result of bacterial inflammations and of traumatic lesions. Injuries and continuous circumscribed pressure without infection may cause periosteal infiltrations (so-called simple periostitis). In mother-of-pearl workers, who constantly breathe the mother-of-pearl dust, there sometimes develops a painful periostitis, the exact genesis of which is not clear.

Ossifying Periostitis.—Here there is produced a mass of new bone, usually called an osteophyte. The inflammation results in the proliferation of the cells in the inner layer of the periosteum, which in their further trans-

¹ Ziegler's *Beiträge*, xvii., 1895.

formation obey the inherent tendency to produce bone; the granulation-tissue changes into osteoid tissue, which by calcification becomes spongy bone. At first but loosely attached, further growth by apposition unites the osteophyte firmly to the old bone and gives it a varying consistence, some being very dense, like ivory. The shape of the osteophytes varies greatly; rounded, pointed, fringe- and leaf-shaped, stalactitic, and other forms are observed (Fig. 208). More extensive diffuse changes may lead to hyperostosis. Ossifying periostitis is a frequent process; it occurs in connection with syphilis, tumors, necrosis, and other bone diseases, in the neighborhood of ulcers (Fig. 211) and articular inflammations, after traumatic injuries and subperiosteal hemorrhages (*e. g.*, the building of a bony wall about the cephalhematoma of newborn children), and sometimes as an independent or "idiopathic" process. In pregnancy, osteophytic formations develop upon the inner surface of the calvaria; usually they are associated with the formation of osteoid tissue in the spaces of the diploe.



FIG. 211.—Osteophyte of the tibia, underneath an ulcer of the leg.

Suppurative Periostitis.—Suppurative inflammation of the periosteum is due to traumatic or hematogenous infections with various pus-producing micro-organisms. The most important form occurs in connection with infectious osteomyelitis.

The inflammation may be circumscribed and lead to the formation of an abscess between the periosteum and the bone; the abscess may break through the periosteal covering and cause phlegmonous inflammation of the adjacent tissue. There may be more or less superficial caries, and even necrosis, of the bone. The details in the periosteal changes of osteomyelitis are mentioned in connection with the latter.

Albuminous or Serous Periostitis (Ollier).—

In this form the subperiosteal exudation consists of a viscid, synovia-like fluid containing fibrin, oil-drops, and but few corpuscles; in some cases the fluid may be clear and serous in appearance.

The characteristic feature is the absence of pus-cells. It may be associated with osteomyelitis. The clinical course is usually mild, and it occurs more especially in the young.

Serous or albuminous periostitis is probably either tuberculous or due to ordinary pus-germs. The peculiar morphology of the exudate may depend upon a secondary mucoid degeneration of the pus-cells, upon reabsorption of the leukocytes, or the exudate may be primarily serous, due to the slight intensity in the action of the microbes (Berg¹).

Osteomyelitis and Ostitis.—Acute Infectious Osteomyelitis.—

Usually acute osteomyelitis is the result of a hematogenous infection. It

¹ *Nordiskt Med. Arkiv*, 1892.

occurs especially in the young as a primary, apparently spontaneous affection, characterized by great pain, fever, and symptoms of constitutional infection and intoxication; or it may develop secondarily to the other infectious diseases, such as scarlet fever, measles, pneumonia, typhoid fever, small-pox, etc., and also in the course of septicopyemic processes.

The primary form is usually caused by *Staphylococcus aureus* or *albus*. The secondary form may be caused by the bacteria of the primary disease, either alone or associated with other microbes.

In the primary form the bacteria gain entrance into the circulating blood (where they have been found during the life of the patient—Garré) either from a minute wound or an inflammatory focus of the skin or mucous membranes, and are subsequently deposited in the tissues of the marrow and the periosteum. It is often impossible to locate the point of entrance; it may have been a small pustule in the skin, a subcutaneous abscess, or a wound that has passed by without any notice or of which all recollection has faded away, when the osteomyelitis suddenly sets in.

The factors that determine the localization upon the bone-marrow of bacteria in the blood are, first, the hyperemia and the embryonal character of the blood-vessels in the marrow and the medullary spaces of the growing bones of the young. The new-formed capillary loops and the irregular vascular spaces in the neighborhood of the lines of ossification as well as in the shafts favor the momentary arrest of the current and the implantation of bacteria upon the endothelium. The necrosis of the endothelial cells by the action of toxins may be followed by extravasations that carry the bacteria into the perivascular tissues. In the second place, the localization of the microbes may be induced by slight traumatism to the bone, which causes further hyperemia, necrosis, and small hemorrhages. The bone-marrow is one of the tissues of the body in which foreign elements in the blood are arrested. Quincke and others have shown that the bacillus of typhoid fever may be present in the marrow of bone, especially the ribs, very late in the disease, and even after convalescence has been established.

Experimental osteomyelitis has been produced by injecting cultures of micro-organisms, especially the pyogenic, into the blood and then producing a subcutaneous injury to some bone (Krause, Rosenbach) or ligating an extremity (Ullman¹); it has also been produced by injecting the bacteria into the circulation of young animals, without the addition of the traumatism; most frequently the inflammation then appears near the intermediary cartilages of bones the seat of active growth (Jordan, K. Müller). In older animals the bacteria are more likely to be deposited in the internal organs and in the joints.

Osteomyelitis in association with pyemia, and also in other instances, may depend upon the arrest in the vessels of the marrow of infected larger emboli.

In most cases a single focus of disease develops. The various bones are attacked in the following order of frequency: femur, tibia, the bones of the upper extremity, the flat and short bones. Occasionally primarily multiple localizations are observed; in 700 cases, Funke found more than one bone affected in 37 instances; in these it concerned mostly two foci, the involvement of three or more bones being rare. At times new foci arise that must be looked upon as secondary to the first focus.

¹ *Osteomyelitis acuta*, 1893.

The inflammation may begin either in the periosteum or in the medullary tissue. Acute periostitis begins with hyperemia, followed by exudation and purulent infiltration; the membrane becomes thick, red, moist, and easily separated from the underlying bone. The pus may be mixed with blood, and, as infiltration and softening increase, subperiosteal abscesses form; the process may invade the parosteal connective tissue, leading to purulent infiltration and necrosis, which may extend along the muscular interstices into the subcutaneous tissue. In virulent infections the periosteum rapidly becomes friable, disintegrated, and discolored, often grayish or yellowish green; in a short time it may be loosened from the bone over extensive areas, which undergo necrosis because deprived of nutrition. The interference with nutrition may involve only the subperiosteal layers, the necrosis remaining superficial; but the inflammation may follow the tissue in the Haversian canals and spaces (osteomyelitis), and the purulent exudate causes compression and thrombosis of the vessels, so that segments of the shaft, and even the whole bone between the epiphyses, may suffer an acute necrosis. When the process is less intense, so that necrosis does not at once ensue, there is usually more or less caries of the bone under the pus.

Acute osteomyelitis begins with hyperemia and often hemorrhage of the marrow, followed by exudation which, at first serous or hemorrhagic, rapidly assumes a purulent or putrid character, giving rise to turbid, yellow, or variously colored soft foci, surrounded by zones of redness. Larger and smaller abscesses may form. In severe instances the purulent inflammation extends diffusely throughout the marrow, and the spaces of the circumjacent spongy and compact bone may be filled with pus; an acute purulent periostitis may follow, from which the inflammation may spread to the soft parts.

The extent and intensity of the process lead to varying degrees of necrosis. If the inflammation is confined to the marrow, there may result necrosis of the internal layers of the bone. Death of the central part of a whole segment of the shaft is known as central necrosis. Involvement of the marrow and of the periosteum may, when diffuse, lead to necrosis of the shaft or of the whole bone. In young bones extensive osteomyelitis of the epiphyses or of the ends of the diaphyses may destroy the intermediary cartilage and give rise to epiphyseolysis. This event is possible up to about the twentieth year; after that time the cartilage has usually disappeared. Epiphyseal osteomyelitis frequently leads to infection of the adjacent joints and synovitis.

The metastatic forms of osteomyelitis are usually not so intense as the primary; the resulting destructions and necroses are consequently smaller. This is especially true in the post-typhoid osteomyelitis, particularly when due to the typhoid bacillus only. Here the pus is thinner, of a darker color, more like bloody serum, and often the process is of a chronic nature from the beginning. The serous or albuminous periostitis, which is sometimes associated with osteomyelitis, has already been referred to.

The terminations of acute osteomyelitis and periostitis vary much. Recovery without destruction of bone is possible when the process is arrested in its beginning, either spontaneously or by means of efficient surgical treatment. Necrosis and sequestration are frequent results. The inflammation may be associated or followed by metastatic abscesses and pyemia, of which the osteomyelitis is simply a part, or the pyemia may be secondary to suppurative thrombophlebitis in the course of osteomyelitis.

In a large number of instances the acute symptoms gradually subside and chronic local suppuration remains, which in course of time may induce amyloid degeneration of the internal organs. Recidivation due to persistence of bacteria or to reinfection also occurs.

Infections in the course of surgical operations, in consequence of puncture and bullet wounds, compound fractures, in amputation stumps, and the like, may cause osteomyelitis. The marrow becomes more or less extensively infiltrated with pus, and partial necroses are frequently produced. The so-called felon is a suppurative periostitis of the distal phalanges, due usually to infected wounds; it is often associated with partial or total necrosis.

Chronic Suppurative Osteomyelitis and Necrosis.—Chronic suppurative osteomyelitis usually represents the further course of an acute infection. There are occasional suppurative infections of the bone-marrow that pursue a more chronic course from the beginning, *e. g.*, some of those due to the typhoid bacillus. They are characterized by the presence of more or less granulation-tissue, by absorption and sequestration of the necrotic material, and by the production of new bone. The further extension of the suppuration is limited by the granulation-tissue produced by the periosteum and the bone-marrow, but the presence of dead bone hinders the rapid closure of the defect.

The necrotic bone or sequestrum resembles normal bone, but is lighter in weight, white, dry, and free from fat; and, unless it was sclerotic or carious before necrosis occurred, the dead piece cannot be distinguished from ordinary macerated bone. The sequestrum usually lies surrounded by pus, and, as long as this is the case, it does not undergo absorption. If closely encircled by healthy granulation-tissue, it is gradually absorbed.

Usually the periosteum and medulla produce new bone around the sequestrum. Sometimes a complete capsule or involucrum is formed around the dead piece. The new bone strengthens and maintains the continuity of the old, especially in the case of total necrosis of a shaft. Externally the involucrum is covered with periosteum; internally it is clothed with granulation-tissue. In the beginning it is soft, porous; later it becomes very hard, the surface often extremely irregular and tough. Total necrosis usually gives rise to the greatest amount of proliferation of the bone-forming tissues. Central necrosis may give rise to great sclerosis and thickening of the surrounding bone.

The involucrum is nearly always perforated by various openings and passages—cloacæ—that give exit to the pus. These openings often communicate with fistulous tracts that open upon the surface of the skin.

If the necrosis involves the superficial parts of the bone, the dead layer is exfoliated by the growth of granulation-tissue between it and the bone. Subsequently the defect may be completely filled and the process permanently healed.

When sequestra enclosed in an involucrum are removed, either spontaneously or surgically, then the bony case often fills rapidly with granulation tissue, which changes into cicatricial tissue or into bone which may be extremely sclerotic.

When such processes occur in the vicinity of an intact intermediary cartilage, not only hyperostosis (Fig. 212) of the bone, but also an abnormal growth in length, may result. In other cases the destruction of the intermediate

cartilage leads to arrest of further growth in length. This may be followed, in the case of the forearm and the leg, by a compensatory hypertrophy of the adjacent bone. In the case of sclerosis and hyperostosis, resorption and apposition may in the course of time restore the bone to a shape more nearly normal.

The so-called *phosphorus necrosis* is a chronic, or rarely acute, periostitis of the facial bones, especially the jaws, of persons who are exposed to the local action of the fumes of phosphorus, as workers in match factories.

The disease attacks mostly individuals with carious teeth, and begins usually as a plastic periostitis, followed by various degrees of necrosis and suppuration, due to infection through the teeth. The dead bone becomes gradually separated from the living by rarefaction. In the meantime an extensive involucrum is produced, while the old bone becomes dense and sclerotic.

Phosphorus necrosis is consequently not entirely a specific process, but due to infection, through carious teeth, of a periosteum which is subject to the stimulating influence of the phosphorus fumes. Uncomplicated, the action of the fumes would cause simply an ossifying periosteal proliferation. Experimental phosphorus necrosis has been produced by Wegner¹ by exposing rabbits to the fumes of phosphorus.

Rarefying Ostitis.—Rarefying ostitis is characterized by the development of a vascular granulation-tissue in the medullary spaces and canals, associated with lacunar absorption and canalization of the bone, which becomes porotic and soft. Rarefying ostitis is a secondary process, and occurs in the neighborhood of necrosis in bone, of tuberculous and osteomyelitic foci, and in the fungous form of bone tuberculosis.

Many writers include under this term processes of absorption that are manifestly not due to inflammation, as, for instance, the absorption due to pressure, uncompensated normal absorption as in rickets and marantic atrophy; and the distinction between rarefying ostitis or inflammatory osteoporosis and caries is not always clear.

Caries is a chronic process, marked on the one hand by proliferation of inflammatory tissue, and on the other by complete disintegration of the bone-tissue, so that actual defects of the surface of bone result. It is also a secondary process that occurs in connection with acute and chronic osteomyelitis, with tuberculosis (the most frequent cause of caries), syphilis and actinomycosis, and in the bone-ends of joints the seat of suppuration and

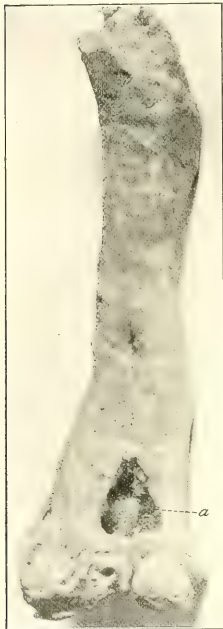


FIG. 212.—Chronic osteomyelitis of the femur, showing great hyperostosis of the entire bone: a, cloaca.

¹ *Virchow's Archiv*, lv., 1872.

tuberculosis. It may be associated with the formation of pus, but not necessarily (*caries sicca*).

In active suppuration and when the granulation-tissue is of low vitality, as in caseating tuberculous foci, absorption of bone does not take place to any extent; the intra-osteal, disintegrating granulation-tissue causes the direct death of smaller particles of bone by interference with its nutrition, and the products of the inflammation and degeneration are mixed with small, partly calcified, partly decalcified particles of bone, or bone-sand. This is the molecular necrosis of bone of von Volkmann. When a gradually extending caries encircles a larger district of bone and thus deprives it of nutrition, the larger sequestrum that forms is said to be the result of *caries necrotica*. While von Volkmann believed that in caries the bone is disintegrated by the chemical solution of the ground substance and the liberation of the calcareous particles, Billroth regarded the absorption of the bone by the cells of the granulation-tissue as the essential factor.

Condensing Ostitis; Osteosclerosis; Sclerotic Osteomyelitis.—Con-



FIG. 213.—Thick skull composed of compact bone. From a syphilitic woman with gumma of the hypophysis.

densing ostitis is characterized by the formation of new, genuine bone by apposition upon the old trabeculae, so that the spaces in the interior of the bone become more or less obliterated, while the bone itself becomes densely sclerotic and perhaps eburnated.

Osteosclerosis may be a secondary process; it may be restitutive and follow an osteoporosis, restoring the normal consistence and density of the bone. It is often associated with ossifying periostitis, and is frequently observed around the central sequestrum of osteomyelitis, around bone-abscesses, in the vicinity of chronic joint suppuration, about tuberculous areas, etc., and corresponds somewhat to the formation of the limiting membranes of connective tissue in suppuration in soft parts.

Osteosclerosis may occur as a more primary process. As such, it is observed in connection with syphilis (Fig. 213). Phosphorus may also induce sclerosis directly. Garré and others have shown that in rare instances infectious osteomyelitis may assume a proliferating form and lead to sclerosis

and hyperostosis of the bone, that may precipitate diagnostic mistakes, the inflammatory enlargements being mistaken for tumors.

Ostitis Deformans (James Paget¹).—This disease occurs in individuals past forty, and oftenest in advanced age. Accompanied by moderate rheumatic pains, there gradually develops an irregular nodular thickening of various bones, together with increasing curvatures and deformity of the parts most exposed to pressure by the weight of the body, namely, the spinal column and the legs. About 60 cases have been recorded; 7 occurred in America (Osler).

The process usually involves several bones, and oftenest those of the lower extremity, the spinal column, the clavicles, and the calvaria. The base of the skull may be pressed upward into the cranial cavity, under the influence of the weight of the head resting against the spinal column. The calvaria is often enormously thickened and enlarged in volume.

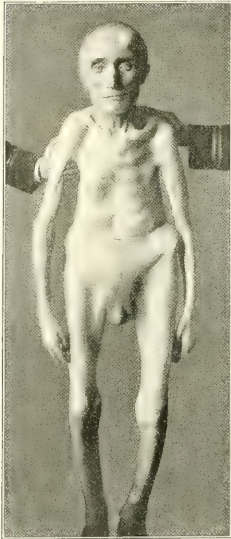


FIG. 214.—Packard's case of ostitis deformans.

According to the microscopic studies of von Recklinghausen² and H. Stilling,³ the disease begins with the absorption by means of Howship's lacunæ and Volkmann's canals, and the bone may become very spongy, porous, and even cystic. Simultaneously there occurs growth by apposition from the periosteum and the medulla; but the osteoid tissue often remains uncalcified for a long time, so that deformities develop. The osteoplastic processes may lead to enormous thickenings; thus, the calvaria may measure between 2 and 3 cm. in thickness. This reconstruction takes place without any regard to the normal internal architecture of the bone, as shown by the fact that in the skull the limits between the external and internal tables and the diploe disappear completely. The process may finally come to a standstill by the occurrence of calcification.

The nature of ostitis deformans, or Paget's disease, is not understood. Richard and Ziegler looked upon it as the same process that occurs in the joints in arthritis deformans, while von Recklinghausen speaks of it as a fibrous osteoplastic ostitis allied to osteomalacia.

Craniostenosis, Hyperostosis Cranii, or Leontiasis Ossea (Virchow).—In this rare and remarkable disease the bones of the face and of the cranium are the seat of a hard, extensive, often enormous hyperostosis. Lobulated masses form especially upon the lower jaw and the lower margins of the orbits, which give the patients a leonine appearance. The cavities in the skeleton of the face and the cranial cavity, as well as the fissures and the foramina, become contracted, due to hyperostosis. Smaller openings may become closed completely. The dried skull, that normally

¹ *Med.-Chi. Transactions*, vol. lx., 1877.

² *Festschrift für Virchow*, 1891.

³ *Virchow's Archiv*, cxix., 542, 1890.

weighs 1 kilo may increase to as much as 5 kilos or more. The narrowing of the canals through which the nerves pass causes pressure, atrophy, and necrosis, and there may result blindness, deafness, anosmia, etc.

Hypertrophic Pulmonary Osteo-arthritis.—This disease was first described by Bamberger.¹ Subsequently Marie² separated the disease from acromegaly, with which it had been confounded in some instances, and gave it the present name.

In well-marked instances the hands and feet are greatly enlarged; the terminal phalanges are characteristically club-shaped, like drumsticks; the nails large, incurvated, not unlike a parrot's beak; the long bones of the forearm and of the leg show a striking increase in size toward the epiphyses, more particularly the distal ones; while the skull and face, as well as the soft parts in general, are practically normal. Not infrequently tuberculosis of the spine has been present, giving rise to deformities, which have, however, as a rule, been located in the dorsolumbar region. Joint-effusions are common (Thorburn).

The relation of this group of symptoms to ordinary hypochondriac fingers—whether the one condition is a more advanced grade of the other—cannot be definitely stated (Thayer³).

From this outline of the appearance, it will be seen that hypertrophic pulmonary osteo-arthritis presents marked differences from acromegaly. The anatomic investigations of Bamberger and others have also failed to disclose any hypophyseal enlargement. In practically all cases there has existed chronic pulmonary or cardiac disease, to which the bony and articular changes are regarded as secondary. The joint-changes consist of erosion of the cartilages and of increase in the amount of synovial fluid, while the bones affected are the seat of proliferating and ossifying periostitis and a condensing or rarefying osteomyelitis. Arnold has consequently proposed the term secondary hyperplastic osteitis as a conservative name for this peculiar process.

Of 55 cases analyzed by Thayer, 43 were preceded by pulmonary affections, 3 followed syphilis, 3 heart disease, 2 chronic disease, 1 spinal caries, and 3 unknown causes. Thorburn looks upon the osteo-articular changes as of a benign tuberculous nature, but no one has as yet demonstrated the actual presence of tubercle bacilli or of tuberculous histologic lesions in the diseased joint- and bone-structures. The bony and articular changes observed may perhaps in some cases be due to tuberculous, syphilitic, or other forms of specific infection; but it is quite likely that in the larger number of cases the osteo-articular alterations depend upon the absorption of toxic substances from lesions of the respiratory apparatus and an elective action on certain parts of the bones and of the articulations (Marie), aided by venous hyperemia, which would seem to be the essential factor in the cases secondary to uncomplicated cardiac diseases.

Tuberculosis of Bones.—Tuberculosis is the most frequent disease of bones. In the majority of cases it is a circumscribed process due to hematogenous invasion by the tubercle germ. Clinically tuberculosis of the bones and of the joints (the bone tuberculosis usually extends to the latter) is often the primary manifestation of the tuberculous infection. Actually, however, it is probably always a secondary metastatic localization, the

¹ *Zeitschr. f. kl. Med.*, xviii., 1890.

² *Revue de Méd.*, x., 1890.

³ *New York Med. Jour.*, 1896.

primary focus or foci in the lymphatic glands or the lungs and elsewhere not being revealed by the clinical examination ; and not infrequently the anatomic investigation may fail to demonstrate primary foci, the possible existence of which in latent or healed form is therefore excluded.

Our general knowledge of tuberculosis teaches that the bacillus may be introduced by inhalation, through the food, and by implantation upon wounds ; and that there usually follows a primary focus of disease at the point where the bacillus is deposited—most frequently in the lungs—from which an infection of the regional lymphatic glands soon takes place. The bacillus may also be carried by cells directly from the skin and the mucous membranes, to be arrested in the corresponding lymphatic glands, where the first depot is then established.

The occurrence of a primary osseous tuberculosis would mean that the bacillus had been introduced directly into the circulating blood from without, which is not considered as likely in postnatal life.

The frequency with which tuberculosis of the bones and joints arises in early life, the characteristic chronicity of the disease in this location, and the existence of tuberculosis in the family in a large percentage, have led to the hypothesis that in some cases the bacillus gains entrance into the blood through the placental circulation, and that the infection is congenital (Baumgarten). The views concerning the importance of this mode of infection are as yet at variance.

Generally tuberculosis of the bones develops in consequence of the lodgement of but few bacilli. Occasionally larger tuberculous emboli may lodge in the medullary vessels. The eruption of miliary tubercles in the bone-marrow in acute miliary tuberculosis is not of any practical importance, because of the rapidly fatal termination of the disease. The development of osseous tuberculous foci by way of the lymphatics, from tuberculosis of an adjacent joint, is also extremely rare. More frequent is the direct destruction and invasion of the bone-ends of a tuberculous joint. Joint tuberculosis, again, is either secondary to bone tuberculosis, or primary, in the sense that the infection occurs in the same general manner as in the case of bones.

In children the physiologic hyperemia of the epiphyseal ends of growing bones undoubtedly acts as a predisposing moment, and the thin walls, slight contractility, and sluggish circulation of the medullary vessels undoubtedly favor the implantation of the bacilli on the vessel-wall, especially under the influence of slight degrees of traumatism.

Clinically osseous tuberculosis occurs mostly in a benignant, chronic form, with comparatively little tendency to generalization. This is regarded by Baumgarten as due to a lessened vitality of the tubercle germ ; hence there are produced especially the epithelioid and giant-cell tubercles, containing but few bacilli, and characteristic of the slow forms of localized tuberculosis in the joints, bones, skin, and lymphatic glands.

Tuberculosis of bones is usually located in the cancellous substance of the epiphyses of the long bones, the short and flat bones, and rarely in the medulla of the shaft, except in the phalanges and the metacarpal and metatarsal bones, which are not rarely the seat of a tuberculous osteomyelitis.

The process, once established, slowly extends by spreading and by growth of new foci near the old, associated with more or less absorption of the

surrounding bone-tissue. In the case of rapid extension and caseation, with molecular necrosis, the death of larger areas of bone occurs.

Occasionally distinctly wedge-shaped foci, with the base pointing toward the ends of the bones, are found (Fig. 206); regarded as possibly of embolic origin (König¹), they were later shown experimentally by W. Müller to result from the occlusion by emboli of arteries that correspond to end-arteries elsewhere, and they are therefore called tuberculous infarcts (Krause). In man they probably arise from tuberculous emboli from foci in the lungs or the bronchial glands, that open directly into the pulmonary veins. Tuberculous foci may become separated from the surrounding bone by a rarefying osteitis: a wall of granulation-tissue forms, that, as the caseation advances, encloses a more or less softened material, sometimes mixed with necrotic bone—a tuberculous cavity has developed. Under favorable circumstances the granulation-tissue may form a cicatricial capsule, outside of which a restitutive sclerosis of the bone takes place (Fig. 215), absorption of the contents follows, and the cavity becomes filled with cicatricial tissue. In many instances the various changes are accompanied with more or less extensive osteoplastic periosteal proliferation.

The specific tuberculous character of the granulations and the caseous material may be determined by demonstrating the bacilli, usually present in small numbers, and by diagnostic inoculation of animals.

The different combinations and degrees in which the processes are associated give rise to gross anatomic appearances that are separated into the following forms (König):

1. The **granulating focus** (fungous osteomyelitis) occurs as single or multiple, round or cylindric cavities or areas, varying in size from that of a millet seed to that of a pea or a hazelnut. They consist either of grayish-red living granulation-tissue, or, if coagulation necrosis has taken place, the resulting cavities are filled with yellowish-gray cheesy matter or fluid tuberculous pus, in which may be fine spiculæ of bone that may be felt with the finger, or, when smaller, seen with the microscope. The bony wall of the cavity is either soft (rarefying osteomyelitis) or sclerotic (osteosclerosis).

2. The **tuberculous necrosis** (caseous osteomyelitis). When the district of tuberculous osteomyelitis is larger than a hazelnut the bone is usually not absorbed, but remains as a distinct sequestrum, which may be composed of porotic or sclerotic bone, depending upon its condition before the nutrition was interrupted. The sequestrum is yellowish-white or red, according to the contents of the canals and spaces, and it may be separated from the wall of the cavity by a layer of tuberculous granulation-tissue, by caseous material, or by tuberculous pus. If separated by granulation-tissue, this may be so thin that the sequestrum fits the cavity exactly, and, if its shape is irregular, it may be hard to pry it out.



FIG. 215.—Osteosclerosis following tuberculosis in the head of the femur; the tuberculous foci are healed, and consist of masses of scar-tissue in dense bone.

¹ *Die Tuberculose der Knochen u. Gelenke*, 1884.

3. The **tuberculous infarct** (see Fig. 206) has the characteristic conic shape of infarcts in general. The area represents the territory of an artery, and large infarcts require for their production either a large embolus or secondary arterial thrombosis from the place of arrest of the embolus. When the base takes in the articular aspect of the bone, its surface becomes ground off and polished, which would signify almost instantaneous death of the infarct. Around the necrotic bone in the interior there forms gradually a layer of tuberculous tissue, which separates the dead bone from the living.

4. **Diffuse tuberculous osteomyelitis** is a rare form. On the cut surface are large, irregular, often multiple yellowish-white infiltrations, without tendency to definition and containing small foci of softening. The circumscribed character of bone tuberculosis elsewhere is not seen in this variety, which it tends to spread indefinitely and to invade the medullary tissue of the shaft. It may spread through the Haversian canals to the periosteum, with the formation of irregular masses of bone on the outside of the cortical substance.

5. **Acute miliary tuberculosis of the bone-marrow** is a part of acute general miliary tuberculosis. It is characterized by the presence of tubercles in the medullary tissue.

Tuberculous foci in the interior of the bones are not, as a rule, of much clinical significance; but it is the tendency to the extra-osseous extension that gives the bone tuberculosis its importance.

When a tuberculous process reaches the periosteum, a soft, elastic, limited swelling gradually appears on the outside of the membrane. If caseation and softening develop, the resulting abscesses (so called) may travel in the tissue-spaces in the direction of least resistance, transforming the tissue, as they advance, into tuberculous granulations that undergo softening and increase the puriform contents of the cavity. Such abscesses often reach a large size, and yet spring from small osseous foci; reaching the skin, this is often perforated and tuberculous fistulous passages are formed. Uncomplicated, the pus contains no other microbes than the tubercle bacillus. The walls of the abscess are formed by tuberculous granulation-tissue, studded with tubercles of the benignant type and loosely connected with the surrounding tissues and organs. At times adjacent fascia may be diffusely infiltrated.

The contents consist of caseous detritus and comparatively few pus-corpuscles, and sometimes little particles of "bone-sand."

The osteotuberculous foci of the epiphyses of the long bones are often situated so near the joint that, when they come to the surface, they are within the cavity, and tubercle bacilli consequently enter the joint, and either directly or by way of the lymphatic current produce various forms of articular tuberculosis.

Tuberculosis of the periosteum may be primary or secondary to bone and joint tuberculosis. Superficial caries may follow, with or without connection with deep foci.

As already stated, tuberculosis of bones tends to involve the cancellous substance of small bones and of the epiphyses of long bones. In the phalanges and metacarpal and metatarsal bones, tuberculous osteomyelitis leads to the formation of more or less granulation-tissue and to absorption of the bone in the interior, so that the medullary canal becomes large. At the same time there is a continuous proliferation of the periosteum, and the

affected bone assumes a spindle- or flask-shaped appearance, known as *spina ventosa*.

Tuberculosis of the spinal column usually begins in the cortex of the body of a vertebra. The gradual extension of the disease destroys the surrounding ligamentous structures and parts of adjacent vertebrae, so that under the influence of the weight of the body the spinal column gives way (Fig. 216) and the bodies of one or more softened and partly destroyed vertebrae are crushed, and there is formed an angular projection, or gibbus, the apex of which usually points backward. This is Pott's disease. Compression of the spinal cord or tuberculosis of the spinal membranes may follow. The vertebrae most frequently involved are those from the seventh dorsal to the second lumbar. In case the tuberculosis is arrested, osteoplastic processes may fix the vertebrae in the abnormal position. Prevertebral cold abscesses secondary to tuberculous foci in the vertebrae are characterized by their great extent, passing in the muscles to Poupart's ligament and even into the thigh (psoas-abscess). Tuberculosis of the atlas and of the odontoid process, although relatively infrequent, is momentous, because sudden movement of the head may lead to instantaneous death, due to dislocation and fracture, the odontoid process sometimes being pressed into the medulla.

Syphilis. — Congenital.—In congenital syphilis there occur characteristic changes at the junction of the diaphyses and the epiphyses, which are known under the term syphilitic osteochondritis (Wegner¹). The changes are fairly constant, and may be readily visible to the naked eye, but in slighter degrees often recognizable only after microscopic examination. The practical value of the characteristic changes is not to be forgotten because their demonstration in a given case, perhaps otherwise doubtful, warrants the diagnosis of congenital syphilis.

Syphilitic osteochondritis should be looked for at the lines of ossification in the long bones, especially the femur. Upon dividing the bone longitudinally there will be found in the slighter degrees a broader, more irregular line of calcification than normal, with finally zigzag margins and a whitish or pale yellowish color (Fig. 217). Microscopically there are seen irregularities in the zone of calcification and in the size of the medullary spaces. The bone-trabeculae vary in thickness and often contain remnants of cartilage, while the marrow may contain an exceptionally large number of giant cells. In more advanced instances the zone is still broader, its margins more irregular, and the adjacent cartilage softened and swollen; and in severe cases the epiphysis may be enlarged, due to proliferation of the cartilage, and



FIG. 216.—Collapse and curvature of the spinal column after tuberculosis of the vertebrae.

¹ *Virchow's Archiv*, 1., 1870.

separated from the bone by a soft, almost disintegrating, grayish, grayish-yellow, or red tissue of varying extent, which consists of embryonal cells in which may be foci of necrosis. The disintegrating granulation-tissue between the bone and the zone of calcification loosens the attachment of the epiphysis, which becomes easily separated during the manipulations, in which cases the surfaces are covered with granular detritus. Spontaneous epiphyseolysis may occur, due to syphilitic osteochondritis.



FIG. 217.—Syphilitic osteochondritis; the irregular broad line of ossification is well shown. From an infant which died from congenital syphilis.

Acquired.—Acquired constitutional syphilis frequently produces extensive osseous lesions, which are generally late manifestations of the disease. The lesions consist, generally speaking, in periostitis and gummas, in caries, often combined with necrosis, and in periosteal as well as in osteal plastic processes that lead to hyperostosis, sclerosis, and the repair of the defects.

Syphilitic or gummatous periostitis produces circumscribed or diffuse swellings of varying size, composed of round and spindle-shaped cells and a few multinucleated giant cells—the periosteal gumma.

At first hard, the areas subsequently may become soft and elastic, the softening producing a jelly-like, viscid mass, which in some instances may become infiltrated with round cells to such an extent as to assume a purulent



FIG. 218.—Syphilitic periostitis and osteomyelitis of the skull, with multiple perforations of the calvaria.

aspect; or the foci may consist of firm granulation-tissue, which gradually is transformed into cicatricial tissue, enclosing here and there yellowish, caseous masses of necrotic and fatty material; there is marked periarteritis and endarteritis. There is more or less resorption or disintegration of bone

(caries), which may occur when there is no softening. The infiltration extends along the blood-vessels into the underlying bone, which becomes the seat of smaller and larger defects and may assume a worm-eaten appearance. The external periosteum of the cranium, especially of the frontal bone, is the most frequent seat of lesions of this kind, extensive defects in the skull are often produced, and a gummatous or syphilitic pachymeningitis develops, due to extension through the skull from the periosteum. In syphilitic periostitis of the skull (Fig. 218), as well as elsewhere, smaller and larger districts of bone, sometimes extensive, are surrounded by infiltrating granulation-tissue, which undergoes necrobiosis and cuts off the blood-supply to the bone, which then undergoes necrosis. In this manner result sequestra sometimes as large as the palm of a man's hand, which eventually are exfoliated and discharged through openings in the skin. When perforation of the cutaneous covering occurs, mixed infection may take place, suppuration and decomposition follow, and still further advance the destruction, causing suppurative inflammation of the neighboring tissues, *e. g.*, the leptomeninx. The cranium, the tibia, the sternum, and the clavicles are among the more frequent seats of destructive syphilitic processes like these.

Gummatous periostitis may be associated from the beginning with osteoplastic processes that tend to repair the defects as they arise; these form sclerosis of the adjacent bone and extensive secondary osteophytic thickenings around the perforations and superficial defects. The sclerotic bone may, through growth by apposition in the medullary spaces, assume the hardness and density of ivory. This combination of caries, necrosis, and the formation of new bone is characteristic of syphilis, and the various changes described are not infrequently recognized in the sequestra.

Syphilitic periosteal gummas and diffuse infiltrations may heal under the influence of appropriate medication. This is characterized by a complete disappearance of the granulomatous tissue, and the defects in the bone become partially closed, the margins thickened and rounded off by a sclerotic process; the skin may become firmly adherent to the depressions; larger defects are bridged over by dense cicatricial tissue, and at the margins is dense, eburnated, smooth bone.

Osteoplastic syphilitic periostitis is characterized by the production of more or less extensive diffuse or circumscribed osteophytes, which are formed independently of coexisting or preceding caries. They occur especially upon the tibia (Fig. 219) and the skull, but may be present in any part of the skeleton. Sometimes they are oval, sometimes nodular or more



FIG. 219.—Syphilitic osteoplastic periostitis.

flattened elevations, with an irregular surface and of varying density. At times the old bone may be osteoporotic ; at other times thickened, heavy, and stone-hard.

Primary syphilitic osteomyelitis occurs, according to Chiari, in the form of circumscribed multiple nodules consisting of a caseous center surrounded by a gelatinous or more fibrous peripheral zone. The gummas are found especially in the marrow of the femur, the tibia, the phalanges, and in the diploe. They are surrounded by sclerotic bone or lead to absorption of the neighboring bone and predispose to spontaneous fracture.

Actinomycosis.—Actinomycosis, and the closely allied mycetoma,



FIG. 220.—Skeleton of a foot; mycetoma (Madura foot). The phalanges of the big toe are honeycombed and carious.

may involve the periosteum and bone by extension from soft parts. In the maxillæ the ray-fungi, especially in cattle, reach the interior of the bone through the alveolar process, and extensive production of new bone often results. Israel and Murphy describe central actinomycosis of the human mandible. In extension from without, there first results an actinomycotic periostitis, followed by extension into the cortex ; superficial caries is produced, or burrowing into the interior of the bone, which becomes expanded into a honeycombed shell filled with granulation-tissue, as well shown in an

instance of Madura foot in Prof. Hyde's clinic at Rush Medical College, the lesions of which were studied by the late Dr. Bishop.¹ The skeleton of the foot is reproduced in Fig. 220. The skull may be perforated by actinomycosis. In the vertebræ, actinomycosis may produce the picture of a tuberculous caries; but gibbus does not result. Osseous actinomycosis also develops as the result of a metastasis through the blood-current.

Leprosy.—Leprosy may give rise to a specific osteomyelitis and periostitis. At first, vacuolated cells filled with bacilli appear; subsequently inflammatory infiltration and characteristic larger and smaller granulomatous foci develop, surrounded by a moderate degree of osteoporosis (Sawtschenko²). In the destructive form of the extremities (lepra mutilans), caries and necrosis of bone and loss of parts of the limbs, especially the phalanges, occur.

Glanders.—In glanders characteristic nodules of granulation-tissue may form in the periosteum.

Variola.—Chiari³ has described a variolous osteomyelitis in the form of millet-sized to split-pea-sized yellow foci, with gray centers. Microscopically the areas consist of epithelioid cells, a few leukocytes, and a fibrinous exudate with central necrosis. Mallory⁴ found that this osteomyelitis occurs in the majority of the bones of the skeleton in small-pox.

TUMORS.

The primary tumors in the bones are of mesoblastic origin. They develop from periosteum, medullary tissue, and from cartilage. The most frequent secondary tumor is carcinoma.

The periosteal tumors usually spring from the osteogenetic layer and lie between the bone and the fibrous layer of the periosteum; sarcoma usually perforates the latter and spreads out into the surrounding tissue. The underlying bone may disappear more or less in consequence of lacunar resorption.

The central tumors develop as circumscribed or diffuse growths from the medullary spaces and the bone-marrow; the bone around the growing tumor usually disappears by lacunar absorption. In the case of benign neoplasms, a dense layer of new bone may form around the tumor, limiting the growth. There is usually absorption of the bone immediately around the neoplasm, and formation of new bone in the periosteum, so that the tumor becomes enclosed in a bony box or case—which is the more complete the slower the growth (Fig. 221). The resulting case of bone is especially complete in myelogenous giant-cell sarcoma. More malignant and rapidly growing tumors may cause absorption to proceed at a quicker rate than production, and thus perforate the surrounding bony encasement.

At the same time as primary tumors of bone cause absorption in their immediate vicinity and new formation of bone in the periosteum, they are also characterized by a frequent tendency to ossification in their interior. In secondary carcinoma of bone the framework may undergo ossification. Osteogenesis in neoplasms of bone may lead to the formation of irregular masses and bits of bone and osteoid tissue, or it may produce a more or less elaborate skeleton within the tumor, as occurs in osteosarcoma, in the form

¹ *Jour. Cutan. and Genito-Urin. Dis.*, 1896.

³ *Ibid.*, ix., 1891.

² *Ziegler's Beiträge*, xiii., 1895.

⁴ *Zeitschrift f. Heilkunde*, xv.

of radiating spiculæ and sheets of bone. True ossification of tumors of bones is not to be confounded with calcification, which may take place in degenerated and necrotic areas.

The exact causes of tumors of bones are not known. Statistics show that trauma favors the development of sarcoma, and quite a number of cases of sarcoma as well as chondroma have developed in the callus of fractures (callus-tumors). Virchow and others have shown that in many instances chondroma can be traced to irregularities in ossification, depending upon a rickety basis.

Sarcoma.—Sarcoma is the most important and the most frequent form



FIG. 221.—Bony framework of an osteosarcoma of the head of the tibia.

of tumor in bone. Two principal varieties are recognized, namely, the central or myelogenic, and the peripheral or periosteal.

Myelogenic Sarcoma.—The central or myelogenic sarcoma may present itself in a number of histologic forms, among which the following are the more frequent :

1. *Myeloid or central osteosarcoma* is usually a mixed-cell tumor, characterized by the presence of a large number of multinucleated giant cells (tumeurs à myeloplaxes—Nélaton) ; in addition there may be large or small round or spindle-shaped cells, and a varying amount of fibrous stroma and of blood-vessels. As the tumor grows it causes absorption of bone around its periphery, and, approaching the periosteum, there are initiated osteo-

plastic processes that provide the growing tumor with a more or less perfect bony encasement, while the tumor itself may produce more or less bone or osteoid tissue in its interior.

Myeloid sarcoma with giant cells occurs most frequently in the lower and upper jaws, in the epiphyses of the long bones, especially of the tibia, and more rarely in the diaphyses.

2. *Richly cellular, round, or more rarely spindle-cell sarcomas* often grow very rapidly and cause extensive enlargements. In some cases there is little or no production of new bone, and spontaneous fractures occur (Fig. 222). As the rapidly growing tumor expands, the bony case-ment that may form becomes thinner and thinner, and often yields with a crackling noise to the pressure of the finger. In many instances there is an extensive production of new vessels and spaces—telangiectatic sarcoma—that dilate and give rise to pulsations and bruits that simulate aneurysms (bone-aneurysms).

3. In *alveolar sarcoma* the cells arrange themselves in small groups or nests within a well-developed connective-tissue stroma, presenting at first glance a microscopic picture not unlike some forms of carcinoma. Alveolar sarcoma of the bone-marrow has been observed to occur as primarily multiple tumors in the cranium, vertebræ, ribs, and sternum.

Myelogenous sarcoma, especially the rapidly growing, richly cellular round- or spindle-cell forms, are liable to various retrogressive disturbances, such as mucoid and fatty degeneration and necrosis. The new-formed thin-walled vessels may give rise to extensive hemorrhage into the tumors. On account of the degenerative changes, as well as from the hemorrhagic extravasations, larger or smaller cystic cavities may develop; the extravasated blood may cause areas of pigmentation.

The central tumors are usually solitary, although exceptions occur. Myelogenic giant-cell sarcomas of the jaws have little tendency to metastasis. The central sarcomas of the long bones are more malignant, both as regards extension to the soft parts and as to the formation of distant (pulmonary) metastases. A limb amputated on account of sarcoma should be carefully examined as regards the condition of its veins, in order to be able to form some idea as to the prognosis.

4. *Myeloma*.—Occasionally the bone-marrow becomes the seat of primarily multiple tumors, either in the form of nodules or as diffuse infiltrations, which consist of wide blood-spaces, without definite walls, surrounded by diffuse areas of round cells, with large nuclei dispersed in a finely fibril-



FIG. 222.—Sarcoma of the femur, with pathologic fracture.

lated, delicate network of connective tissue. Wright¹ shows that the majority of the cells correspond closely to plasma-cells. The old bone in the vicinity of the nodules and infiltrations, which occur more frequently in the cranial bones, the ribs, the sternum (Fig. 223), the vertebræ, as well as elsewhere, disappears, while but little new bone is formed, so that the growths often break through and infiltrate the periosteum and the surrounding tissue. Some authors designate this tumor as angiosarcoma, as lymphosarcoma of bone, as lymphadenia ossium (Nothnagel), as general lymphadenomatosis of bone (Weber²), and as myeloma (von Rutizky, Klebs, Herrick and Hektoen³). They are regarded by Klebs as infectious medullary lymphomatous swellings, and belong perhaps to the pseudoleukemic diseases of the

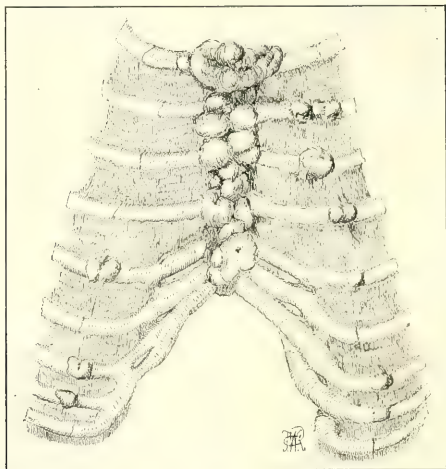


FIG. 223.—The sternum and ribs, showing the location of myelomatous growths (Herrick and Hektoen's case).

marrow, but their exact onkologic and etiologic relations have not yet been established.

Periosteal Sarcoma.—The periosteal sarcomas occur in any part of the skeleton, but are observed more frequently at the ends of the long bones. They are of soft or hard consistency, presenting a homogeneous, fibrous, radiating surface; or the degenerations, hemorrhages, and necroses that occur, especially in the softer forms, may give to the cut surface a mottled appearance. Histologically they belong usually to the round- and spindle-cell varieties, but giant-cell as well as mixed-cell periosteal sarcomas are not infrequent. Alveolar periosteal sarcoma also occurs. The large spindle-cell sarcoma often shows transition to fibroma. The sarcomatous epulis is usually a spindle-cell or mixed-cell periosteal sarcoma.

Periosteal sarcoma may present a nodular growth that in the beginning

¹ *Jour. Boston Soc. of Med. Science*, iv., 195-204, 1900.

² *Jour. of Path. and Bact.*, v., 59, 1898.

³ *Medical News*, 1894.

has a spindle-shaped form and tends to embrace the bone. Later on it may break through the periosteum and spread into the adjacent tissues. The underlying bone becomes rarefied and infiltrated with tumor-tissue, so that spontaneous fracture takes place; or it also happens that the contiguous bone is changed by an "ossifying osteomyelitis" into the densest sort of a structure. The tissue of the tumor itself may produce new bone, and there may be formed an osseous base, resting upon the bone from the periosteum of which the tumor springs, while massive exostoses or finer spiculæ and needles of bone project in a radiating or stalactiform manner into the tumor-mass (osteosarcoma, ossifying sarcoma). At other times the production of bone may be more limited, irregular needles and masses being formed, or perhaps only osteoid tissue without any calcification (osteoid sarcoma). The metastases of such sarcomas may undergo ossification.

Combination forms of chondrosarcoma, osteochondrosarcoma, etc., are also observed.

Of the periosteal sarcomas, the softest and most cellular are undoubtedly the most malignant. The metastases are more frequent than in the myelogenic sarcoma, and are usually first observed in the lungs.

Fibroma.—Fibroma of bone is a rare tumor, usually of periosteal origin. It occurs most frequently in connection with the bones of the mouth and nasopharynx, where it forms a part of the tumors that clinically pass as fibrous pharyngeal and nasal polypi and as epulis (fibrous epulis). The distinction between periosteal fibroma and sarcoma is not always possible. Periosteal fibromas are sometimes vascular and telangiectatic; bone-tissue may also be produced in their interior (osteofibroma, ossifying fibroma).

Chondroma.—Chondroma of bones arises from misplaced islands of cartilage in bone (Virchow), or from the periosteum or medulla. In many chondromas a history of rickets is obtainable; the resulting disturbances of ossification may furnish the cartilaginous matrix for the frequently multiple tumors. In other cases the tumors develop from misplaced remnants of the transitory cartilage, due to unknown or hereditary conditions (Nasse).

Chondroma may be peripheral or central, multiple or solitary. It is observed most frequently upon the diaphyses of the phalanges in children and young persons, but also at the epiphyseal line of the femur, as well as in connection with the pelvis, scapula, and ribs. It usually consists of hyaline cartilage, and presents itself as lobulated tumors composed of larger and smaller masses of avascular, bluish-white cartilage, surrounded by a vascular perichondrium and subdivided by fibrous tissue. Chondroma may undergo myxomatous degeneration of the intercellular substance and become a myxochondroma, or there may result total softening with the formation of cystic spaces; petrification may take place, as well as true ossification (osteochondroma, ossifying chondroma). Pure chondromas occasionally, though rarely, form metastases. Chondrosarcomas also occur.

The so-called osteoid chondroma (Virchow, Volkmann) is a peculiar tumor in which osteoid trabeculæ from the osteogenetic layer of the periosteum grow in all directions, often producing large tumors, occurring mostly near the ends of the long bones of young persons (femur, tibia, humerus). The surface of the growth is usually smooth, and the cut surface partly hyaline and transparent, partly lamellated and reticular. Partial or complete ossification may occur. Metastases have been observed in such tumors. Osteoid chondroma is closely related to osteoid sarcoma.

Ecchondrosis is an outgrowth from normal cartilage. Simple ecchondroses are small outgrowths that remain cartilaginous; they are observed in connection with the ribs, the laryngeal and auricular cartilages, etc., of old people. From the sphenobasilar synchondroses arise small, soft tumors, the cells of which become changed into vesicles, and hence the growths have been called ecchondrosis physalifera. Virchow regards their origin to be the cartilage of the synchondrosis. Ribbert and others trace them to a proliferation from remnants of the notochord.

The ecchondroses may petrify, undergo mucoid degeneration, or change into bone.

Osteoma.—Exostoses are circumscribed formations of new bone, usually regarded in the light of tumors, although it is frequently hard to separate them from inflammatory osteophytes and hyperostoses. When they arise from the surface of the bone they are called exostoses; if from the interior, enostoses. According to the genesis, a distinction is made between cartilaginous exostoses, which arise from preformed cartilage, and fibrous exostoses, which arise from fibrous tissue. According to the structure, exostoses are divided into compact (*eburnea*), composed of hard bone-lamellæ without medullary tissue, and into spongy, in which there are medullary spaces.

The cartilaginous exostoses occur in connection with bones formed by enchondral ossification, most frequently upon long bones near the epiphyseal line, the ribs, and the vertebrae. They may be oval, nodular, pointed, or hooked, and variously formed outgrowths that develop in direct or indirect connection with the epiphyseal or articular cartilage. They are usually covered with a layer of cartilage, from which the bone is formed (ossifying ecchondrosis). Sometimes the end is covered by a bursa—*exostosis bursata*. Cartilaginous exostoses are also observed in connection with the scapula and the bones and joints of the pelvis. In the latter instance their presence may be of practical obstetric interest (*pelvis spinosa*).

Cartilaginous exostoses usually occur singly, but a number of cases have been described of multiple exostoses developing especially in the period of most active growth (Virchow, Chiari, etc.). In many instances an hereditary tendency has been shown (Heymann, Nasse, and others). In some cases a previous rickets has been demonstrated. The condition would seem to depend largely upon developmental anomalies on the part of the epiphyseal cartilages (Nasse). According to Bessel-Hagen and to Nasse, the skeleton of persons with multiple exostoses usually shows other and quite extensive disturbances of development.

Among the fibrous exostoses the periosteal are directly connected with the periosteum; the parosteal or discontinuous occur independently of and away from the bone. The periosteal may be movable or immovable. The shape and size of the exostoses vary much; they often develop in consequence of traumatic and inflammatory lesions of bone or neighboring tissues. The parosteal occur in tendons, muscles, intermuscular connective tissue, and aponeuroses. The subungual exostosis of the big toe is of special interest, on account of its pressure-effects. Luxuriant callus may lead to the formation of durable enlargements of the bone, especially in lower animals (*osteoma fracture*), due to the new formation of bone from a matrix of postnatal origin. Exostoses of the cranium may consist of compact bone; here they may assume the form of rounded, flat, button-like, or fungoid outgrowths.

Exostoses are found especially in the sinuses and cells of the cranial and facial bones; they may also develop in the diploe of the skull (Virchow¹). From these points of origin the tumor, when it becomes too large for the cavity in which it originated, may enter the orbit, the cranial and other cavities, by pressing upon the bony wall, so as to cause atrophy (Arnold). According to Fenger,² the tumor is originally round, but undergoes modifications as it enlarges and extends into an adjacent cavity; the consistence is hard, like ivory; there may be spongy tissue at the base, extending for a distance into the growth. As the osteoma enters an adjacent cavity it pushes before it the mucous lining of the cavity, and in this way it may lead to intracranial and other forms of suppuration. A growth of this kind may loosen spontaneously, when it becomes known as a dead osteoma (Fenger). Osteomas of the cavities of the head have been referred by Rokitsanski to remnants of the primordial cranium.

Myxoma.—Myxoma and myxofibroma of bones are rare tumors; they may originate either from the periosteum or the marrow, and may be single or multiple. The pure myxomas often liquefy and form cysts. Combinations occur, like myxochondroma, myxosarcoma. Osteomyxoma has also been observed.

Lipoma.—This is an exceedingly rare form of tumor. Sutton collected 9 cases originating from the periosteum and often combined with striated muscle-fibers.

Angioma.—There are only few authentic cases of angioma of bone recorded. Virchow describes myelogenous angioma of the vertebræ. It has also occurred in the calvaria, the femur, and the sternum. Pean has described telangiectatic periosteal angioma of the palate and of the bones of the orbit, Birch-Hirschfeld a combination of chondroma and cavernous angioma in the phalanges, and Lücke records an ossifying angioma in the antrum of Highmore. In the majority of cases the so-called pulsating tumors, genuine and false aneurysms, and cavernous tumors of bone are centrally degenerated cystic or telangiectatic sarcomas.

Cysts and Cystoma.—Bone-cysts usually arise from softening in solid tumors, such as chondroma, sarcoma, and myxoma. Cysts from softening also develop in osteomalacia and osteitis deformans. Parasites, as the echinococcus and *Cysticercus cellulosæ*, may cause cysts in bone. Echinococcus-cysts occur especially in the long, hollow bones, but also in the cranium and vertebræ; something like 50 cases have been described.

Dermoid cysts have been found in connection with the bones and periosteum, especially of the cranium.

True cystoma of bone is rare except in the maxillæ (Fig. 224), where

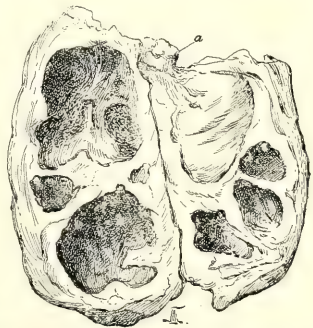


FIG. 224.—Multilocular dentigerous cystoma of the mandible: a, tooth.

¹ *Die krankhaften Geschwülste.*

² *Jour. Amer. Med. Assoc.*, 1887.

dentigerous cystomas that develop from the misplaced matrix of permanent teeth are not infrequently encountered.

Such a case as the one reported by Engel, of a fifty-five-year-old woman, whose entire skeleton was the seat of small and large cysts containing clear fluid or bloody serum, and surrounded by a wall of connective tissue, are hard to understand. I have observed a case of multiple small-cell sarcoma of the bones in which many of the tumors were largely cystic; the yellowish, viscid fluid contained digestive ferments.

Secondary Tumors.—Secondary sarcoma of bone occurs more particularly in connection with melanosarcoma.

Carcinoma of bone is probably always secondary, and in cases of apparently primary osseous carcinoma careful search will usually reveal their secondary nature. The bone may become involved by direct extension when the carcinoma originates in a fistulous tract, in the skin, or other structure

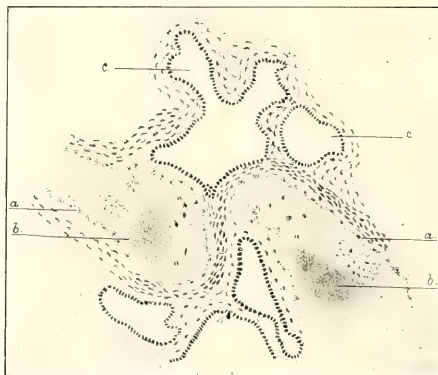


FIG. 225.—Adenocarcinomatous metastatic growth in the scapula, with new formation of bone: *a*, osteoblasts; *b*, calcified osteoid tissue; *c*, glandular tubules. $\times 275$.

adjacent to bone, and there may result a disintegration and absorption of bone in consequence of the carcinomatous infiltration.

Secondary metastatic carcinoma of bone occurs with a relatively striking frequency after primary carcinoma of the breast in women, of the prostate in men, of the thyroid gland, and of the bronchi. It not infrequently is the case that many months and years elapse after removal of the primary tumors before the bone-metastasis is noticed. The vertebræ, femur, ribs, sternum, humerus, cranial bones, etc., are the usual seats of metastasis, the order of frequency being that in which they are mentioned (von Recklinghausen¹). The localization of carcinomatous emboli occurs by preference in the parts of the bones that are subject to the greatest traction or pressure. The histologic character of the secondary tumor always corresponds to that of the primary; the metastatic growths may present circumscribed nodules or diffuse infiltrations. The diffuse infiltrations may cause extensive lacunar absorption of the bone, which becomes soft and easily bent (carcinomatous

¹ *Festschrift für Virchow*, 1891.

osteomalacia—von Recklinghausen), or the growths may be accompanied with the formation of new bone-tissue (Fig. 225) at the same time as the old is absorbed—osteoplastic carcinosis. In the latter instance the carcinomatous cell-nests may be embedded in osteoid or fully calcified tissue, so that the tumor may be hard and firm, and dense on the cut surface. In carcinoma of the breast, with regional metastasis in the axillary glands, a backward lymphatic transport may carry carcinoma-cells into the humerus and give rise to secondary carcinoma.

RICKETS.

Rickets or rachitis is a general disease, which disturbs the growth of the bone because of an insufficient deposit of lime salts at the points of ossification, an excessive production of osteoid tissue, and an increased or uncompensated resorption of the bone already produced.

The disease was first described by Glisson, in England, in 1650. The common people applied the term "rickets" to the disease because of the resulting bone-changes and deformities. This comprehensive and picturesque word is more appropriate than the name rachitis, first used by Glisson,¹ and descriptive only of the occasional vertebral changes that occur in the disease. Rickets is a disease especially of the first two years of life, but may occur as late as the eighth or tenth year.

The disturbances of normal ossification in rickets are present in all parts of the skeleton, and affect as well the endochondral as the periosteal processes. If a rickety long bone be divided longitudinally, the following deviations from the normal can be made out at the lines of ossification:

1. The zone of proliferation is broader than normal; the cartilage is bluish red, swollen, and soft.
2. The linear zone of calcification is irregular, and often indicated only by scattered whitish points.
3. The marrow is hyperemic, and the vascular medullary spaces have penetrated the soft cartilage beyond the line of preliminary calcification; the medullary spaces are irregular.
4. Between the cartilage and hard bone there often lies a layer of osteoid tissue, which may vary greatly in extent—from a few millimeters to one or two centimeters—and which is soft, flexible, and elastic, the epiphyses being swollen.

The microscopic examination shows, in the enlarged zone of proliferation, evidences of an excessive multiplication of the cartilage-cells, because there may be capsules containing 20, 30, or 50 cells and more, arranged in columns; nearer the diaphyses are very large cartilage-cells, without arrangement in rows. Here and there are noticed vascular medullary sprouts in the uncalcified cartilage, often surrounded by osteoid tissue; an abnormal number of vessels also extend into the cartilage from the perichondrium.

Between the changed cartilage and the solid bone lies a layer of uncalcified or irregularly calcified osteoid tissue of varying thickness, composed of irregular trabeculae separated by wide medullary spaces and containing here and there islands of unchanged cartilage. In some of the osteoid trabeculae calcification may have occurred (characterized by staining a deep

¹ *De rachitide*, 1650.

bluish red with hematoxylin and by refusing to stain with ammonium carmin). The osteoid tissue is produced by osteoblasts and by metaplasia of connective tissue in the medullary spaces and in the areas of large-cell cartilage. Osteoid tissue also arises by metaplasia of the cartilage; the metaplasia occurs most extensively near the vessels.

The osteoid tissue is homogeneous or fibrillated, with or without a lamellated arrangement, and contains bone-cells in irregular distribution.

In severe cases the osteoid tissue may be produced to such an extent that the spaces in the existing bone, as well as the medullary cavity, are filled for a certain distance with a callus-like tissue.

The marrow in rickets is usually cellular and red or fetal, even in the bones of the extremities of older children.

The changes in the periosteal ossification consist in the excessive production by the proliferating layer of the periosteum of a lamellated or non-lamellated osteoid tissue, with no or very irregular calcification. The osteoid masses often surround the bone like a periosteal callus or appear as vascular and spongy proliferations of greater or less extent (osteophytes). If one attempts to strip away the thickened periosteum of a long bone, thin pieces of soft, porous bone-tissue are usually brought away at the same time. Osteophytes composed of soft, easily incised, vascular tissue, with at most irregular areas of calcification, occur, especially upon the external surface of the bones of the cranium, but also at other points where the bone grows by apposition. Periosteal proliferation is not necessarily a constant phenomenon in rickets.

Increased or perhaps rather uncompensated absorption of bone already produced also occurs to a marked extent in rickets. It is shown by the formation of unusually wide medullary spaces at the lines of ossification and by an osteoporotic condition of the spongy as well as compact bony tissue in the long bones, while the cranial bones may be absorbed to the extent that in places only a thin layer of osteoid tissue remains (craniotabes). The resorption takes place by means of osteoclasts, and possibly, but to a limited extent, by halisteresis.

Active resorption of bone occurs physiologically during the period of growth; and it is a question not yet decided whether the resorption in rickets exceeds the normal in extent. Pommer¹ and others do not believe the activity of resorption exceeds the normal. The resorption in rickets is not compensated, however, by growth of new bone by apposition, as is the case in health. In rickets there is produced, often in excess, only a noncalcified or irregularly calcified osteoid tissue.

Rickets is consequently characterized by the following deviation from the normal in the development of bones: Irregular and deficient calcification, both of cartilage, preliminary to enchondral ossification, and of the osteoid tissue, in the intracartilaginous as well as periosteal forms of ossification; excessive proliferation of cartilages, and irregular and excessive vascularization in the epiphyses; excessive production of osteoid tissue by the medullary and periosteal structures, as well as by metaplasia from cartilage; and a continuous physiologic or excessive resorption that is not compensated for by the production of new normal osseous tissue.

The pathogenesis of rickets has not yet been fully cleared up. From the study of the histologic changes, it is learned that the absence of calci-

¹ *Osteomalacia u. Rachitis*, Leipzig, 1885.

fication of the osteoid tissue is one of the most important factors or links in the process. It has therefore been suggested that rickets develops because too little salts are introduced into the body by way of the food or absorbed from the intestinal canal; but Vierordt has shown that the absorption of lime salts during the development of rickets is as good as in health, and that increased ingestion of salts is followed by increased elimination by the urine. Improper diet in general, and deficiency of fat in particular, are regarded as important factors.

The real secret of the disease must be sought in disturbances of the osteoblasts and other cells, whose function it is to split up the lime albuminates and cause the infiltration of osteoid tissue with lime. Kassowitz regards the hyperemia as the primary lesion. Rickets is usually associated with morbid gastro-intestinal processes, anemia, leukocytosis, and other blood-changes, chronic enlargement of the spleen, etc., changes that cannot be explained solely by improper diet.

Changes somewhat similar to those of rickets have been produced by the administration of food lacking lime (Roloff); of phosphorus, which is claimed to stimulate the osteogenetic tissues, together with food lacking lime (Wegner); of lactic acid in herbivora (Hofmeister); but these experiments are not directly applicable to rickets in the human being, because here it often arises under conditions diametrically opposite to those produced in the experiments. The withdrawal of mother's milk from young animals and placing them on a diet of meat, vegetables, or starches is usually sufficient to produce typical rickets (Bland-Sutton, Guerin). Perhaps poisons introduced from without or produced in the body, especially in the digestive tract, often associated with vicious alimentation and improper hygienic surroundings, cause the disturbances of osteogenesis of rickets.

When the morbid process of rickets becomes arrested, there follows a gradual calcification of the osteoid tissue. In the course of time the resulting bone undergoes complete resorption, and is replaced by new bone formed according to the physiologic type. Slight degrees of rickets may be followed by a complete restitution. Severe forms of the disease often lead to great deformities on account of the softness of the bones, which is especially marked in the region of the proliferating cartilage, where the bone is flexible. In the shafts the deficient calcification and continuous absorption favor infractions. Bends, fractures, and flattenings may follow, due to weight and muscular action.

Subsequently the swellings at the epiphyseal junctions may remain; the bones often are plump and sclerotic, the medullary spaces becoming almost occluded; the complete ossification of the osteophytes may lead to permanent thickenings; the irregular islands of cartilage scattered throughout the osteoid tissue at the junctions of the shafts of the long bones with the diaphyses may remain, and later in life give rise to enchondroma and cartilaginous exostoses (Virchow). Occasionally rickets is followed by absence of the growth of bone, and the individual becomes subnormal in size, at times of but dwarf-like stature, the extremities being short, but the trunk of normal length (rickety dwarfs).

The following are some of the more important results of rickets in the various parts of the skeleton:

The Cranium.—The fontanels usually remain open, and the sutures fail to close during florid rickets; the cranial part of the head is often large

as compared with the face, the frontal and parietal eminences being especially pronounced; coexisting hydrocephalus will, of course, cause further aggravation of the changes. The periosteal osteophytes or bosses upon the external surface of the cranium may become several millimeters in thickness, and may be converted into sclerotic bone when the process heals. The constant intracranial pressure and the uncompensated resorption of bone may lead to the production of defects in the old bone, closed only by osteoid tissue, and at times covered only by the skin. Such defects are oftenest observed in the occipital region, presumably on account of the additional pressure to which this part is exposed.

The cranium may become permanently changed in form. It may remain permanently large; it can assume a four-cornered aspect, due to

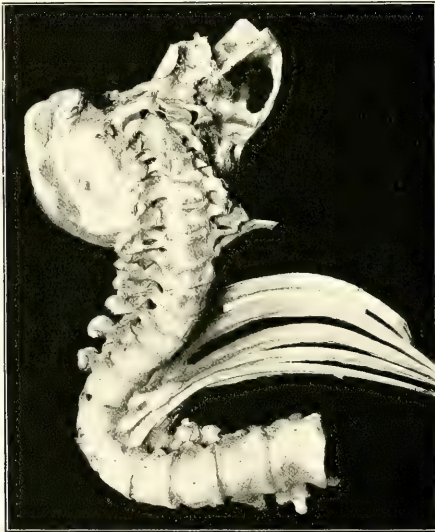


FIG. 226.—Excessive rachitic spinal curvature.

the four areas of ossification in the frontal and parietal bones remaining, as it were, like four fixed points, while the further increase in size occurs by growth at the sutures.

The Spinal Column.—Under the influence of the weight of the body and of muscular action arise spinal curvatures—scoliosis, lordosis, and kyphosis—with the corresponding thoracic deformities (Fig. 226). The spinal curvatures of rickets are, in the main, exaggerations of the normal curves, due to the increased pliancy of the vertebræ on account of the changes in the bone-tissue.

The Thorax.—The symmetric thickenings at the costochondral junctions that occur in rickets, one of the first signs of the disease, are currently referred to as the rosary of rickets.

The lateral and anterior curves of the ribs may disappear, and the sternum project forward like the keel of a ship, with the xiphoid appendix further removed than normal from the spinal column—a characteristic deformity known as chicken-breast or pigeon-breast (*pectus carinatum* or *gallinaceum*). At other times, but more rarely, the sternum, especially the lower end, is depressed toward the spinal column, so that there results a trough-like or funnel-shaped hollow—the funnel-shaped sternum which owes its origin, in some cases at any rate, to rickets.

The Pelvis.—The deformities of the pelvis due to rickets are of pre-eminent obstetric importance. The usual form of rickety pelvis is due to increased projection of the sacral promontory, and is characterized by a shortening of the diameter from before backward (conjugate), while the transverse diameter increases.

The Long Bones.—The epiphyseal regions are usually swollen in active rickets. The epiphyseal ends may, on account of the flexibility of the cartilage, become bent, and characteristic deformities arise (*genu valgum*). Epiphysiolysis may occur. The shaft may bend and curvatures arise, which in the leg usually present the convexity outward, while in the femur the convexity usually points inward. The shaft may break incompletely, or fracture may take place. The infractions cause well-defined deformities in the tibia. Healed rickets often leaves the shaft of the long bones flat, like saber-sheaths, with sharp margins, and sclerotic in structure.

OSTEOMALACIA.

Osteomalacia (*mollities ossium*, *malacosteon*, *halisteresis ossium*) is a chronic progressive disease of adults, characterized by decalcification of pre-existing old bone (*halisteresis*) and by noncalcification of new-formed osteoid tissue, observed most frequently in pregnant or prolific women (*puerperal form*), but also in childless women and in men (*rheumatic form*), and in old age (*senile form*). The disease may occur in sporadic form; but in certain regions, *e. g.*, the Rhine district in Germany, it is endemic. In both cases some of the etiologic conditions seem to correspond; and, according to von Winckler, the following are the more important recognizable causes: Unhygienic, moist dwelling-rooms, insufficient clothing, poor and predominatingly vegetable food, pregnancy, puerperal conditions, and protracted lactation. The disease usually begins with rheumatoid pains in the back and elsewhere, followed by a gradual softening of various bones, and especially those of the pelvis, the spinal column, the base of the skull, etc. In the nonpuerperal form the disease begins oftenest in the spinal column and the thorax.

The histologic changes consist not only in a decalcification of the old bone, but also in the formation of new osteoid tissue which remains uncalcified. The process of resorption of salts in osteomalacia is regarded as commencing at the margins of the bone-trabeculae, where there is formed a homogeneous or striated margin that stains red with carmin and contains more or less irregular bone-cells (Fig. 227). The limits between the decalcified and normal bone may be quite even, or irregular and zigzag; the decalcification may at times begin in the interior of the trabeculae. In the still calcified parts adjacent to the decalcified may be seen granular streaks and lines running in various directions, which are regarded by some as

representing commencing changes preliminary to removal of the lime salts; when decalcification is complete these markings disappear. Canals perforating the bone-trabeculae also appear in considerable numbers, but osteoclasts and Howship's lacunae are not present any more numerous than in growing normal bone. The continuous decalcification may be associated with actual resorption of the ground substance, so that there results enlargement of the Haversian spaces and canals; and in advanced cases there form smooth-walled larger and smaller cysts, filled with mucoid material. Simultaneously or subsequently there takes place more or less extensive formation of new osteoid tissue, which in many instances is quite excessive and which for the time being remains uncalcified. The new tissue is produced by the osteoblasts, and may be quite dense and contain only fine spaces; it may present a lamellated structure, or more frequently an interwoven fibrillated appearance, with large corpuscles. The new tissue is formed most extensively at points of flexion and of fracture of the softened bone; the callus

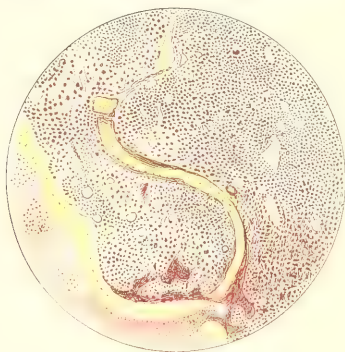


FIG. 227.—Cortex of vertebra; only imperfect trabeculae remain, which in the center show normal bone-structure; but at the margins is a decalcified seam (halisteresis) that stains reddish in van Gieson's mixture. The marrow is cellular and fibrous. $\times 125$.

formation may be prolific, but not followed by calcification. It also forms to an excessive degree at the points where the bone is exposed to mechanic strain, *i. e.*, where strong muscles, tendons, and ligaments are attached. When calcification occurs, it may take place first in the center of the new lamellae (Ribbert¹).

The marrow of osteomalacia is partly hyperemic and red, partly fatty and jelly-like; constant characteristic changes do not occur; it may become quite fibrous.

The exact nature of the histologic changes of osteomalacia are not agreed upon. Some regard the processes of absorption as quite physiologic, and conclude that the changes depend upon the noncalcification of the new osteoid tissue (Cohnheim, Pommer, Hanau). The long duration of osteomalacia—often many years—makes it possible that in some cases the histogenesis consists essentially in a faulty appositional growth of otherwise normal bone. The presence of medullary spaces wider than normal, between

¹ *Osteomalacia*, 1893.

trabeculae consisting partly of calcified, partly of noncalcified tissue, indicates the occurrence of halisteresis. On the other hand, there can be no question that new osteoid tissue is formed to a greater extent than has been thought; and the density of its structure, its nonlamellated arrangement, and its appearance at certain preferred places show that it is formed in excess and contrary to the normal type. New-formed osteoid tissue is easily distinguished from decalcified old bone, as it contains larger, better-formed cells. Osteomalacia has, in common with rickets, deficient calcification of new osteoid tissue; but it cannot well be regarded as dependent on the same causes, on account of its progressive character and its occurrence in adults; whereas rickets is a disease of infancy that is usually recovered from.

Formerly, when osteomalacia was regarded as due to absorption of lime, its cause was sought in the production of an abnormal amount of acids, on account of digestive disturbances; but of late the opinion has become prevalent that the disease is an active process, depending upon disturbance in the blood-supply and innervation of the medullary tissue, due to inflammatory stimuli (Volkmann) or to arterial hyperemia (von Recklinghausen, Fehling).

Hanau has shown that in 25 to 30 per cent. of puerperal women osteophytes and osteoid zones are present in the cranial bones. The occurrence of this slight osteomalacia under physiologic conditions would seem to indicate that puerperal osteomalacia may be regarded as an aggravation of a normal process (Birch-Hirschfeld). The demonstration of a puerperal physiologic osteomalacia has probably destroyed the value of the experiments of Stilling and von Mering, in which a slight grade of osteomalacia appeared to be produced by feeding, to a pregnant bitch, fat, free from meat, and distilled water.

The relation of osteomalacia to the generative organs of women has been further demonstrated by the reports of Fehling and others of the recovery from the disease by removal of the ovaries. Fehling constructed the theory, basing his reasoning upon his favorable experience in connection with castrated patients, that osteomalacia depends upon a reflex stimulation, from the ovaries, of the vasodilators of the bone-vessels, resulting in hyperemia and halisteresis; upon the removal of the ovaries, the reflex vascular dilatation disappears and the changes cease. The ovaries have also been described as large and bloody in osteomalacic patients. Rossier also looks upon puerperal osteomalacia as an ovarian trophoneurosis. Zweifel is of the opinion, however, that castration is beneficial only in the degree that it prevents new pregnancies.

While osteomalacia in its typical form is a progressive disease that terminates only with the death of the patient, cases occur in which the process is arrested and healing follows; calcification of the dense, new-formed osteoid tissue may render the bones sclerotic and heavy.

The resulting malformations during the progress of the disease are referable to the great softness and friability of bones acted upon by the body-weight and muscular contraction. The spinal column may become the seat of various curvatures; the sternum and the ribs, of bends and fractures. The long bones of the extremities are more rarely involved, in the degree characteristic of the flat bones; when the softening is extensive, they become extremely deformed and the seat of frequent fractures and infractions. The pelvis may become the seat of contractions and deformities.

THE JOINTS.

MORBID CHANGES IN CARTILAGE IN GENERAL.

Retrogressive Changes.—Various degenerative changes occur in cartilage. The cells may undergo fatty degeneration in consequence of old age and local circulatory disturbances. The so-called senile or mucoid softening of cartilage is rather a complex change; it occurs in the costal as well as in the articular cartilages, in chronic forms of arthritis, and in the cartilages of the synchondroses. The ground substance becomes fibrillated or cracks into flakes and detritus, followed in some cases by a mucoid softening, while the cartilage-cells may proliferate and form irregular heaps, surrounded by many-layered, refractile capsules; necrosis of the cells also occurs; crevices filled with fluid, or small cystic cavities, are sometimes produced; in other places, calcification gives rise to white areas. In the beginning these changes produce glistening, whitish, striated areas, like asbestos; later the cartilage becomes yellow, brownish yellow, or gray, and transparent, in circumscribed spots or more diffuse areas; calcification renders it white and opaque. Degenerated areas situated near bone may become filled with blood-vessels, cells, and spongy bone; ossification also takes place from the perichondrium. At other times the softened foci are filled with fibrous tissue; the surface of the articular cartilage becomes velvety, and the friction may cause more or less extensive loss of substance.

In old age hyaline or amyloid degeneration sometimes develops in the cells, the capsule, and matrix of the cartilage of joints and synchondroses. There results a bluish-yellow, spotted appearance in amyloid degeneration; under the microscope the capsules are hyaline and swollen, the cells and matrix change into irregular scales and fragments.

Calcareous infiltration occurs, especially in degenerated areas; it is rather frequent in old age, and the calcareous particles are deposited in the capsules, cells, and the matrix. In the case of the articular cartilages of chronically inflamed joints, the petrification is most marked along the margins. In gout urates are precipitated into the ground substance and the cells (gouty or uratic arthritis). After hemorrhage into a joint-cavity, or in case of jaundice, hematoidin crystals may be found in the articular cartilages.

Ochronosis is a rare form of brown or black pigmentation of cartilages, tendon-attachments, joint-capsules, etc., of unknown origin (Virchow,¹ Hanse-mann²). According to Marchand, cartilage placed in formalin acquires a similar color.

Progressive Changes.—Metaplasia.—If the ground substance of cartilage is changed, while the cells persist, then these may be retained as part of the substituting tissue. Most frequently metaplasia results in the formation of mucoid tissue. True metaplastic ossification occurs either as a senile change (in the laryngeal cartilages) or as a post-inflammatory process. Cartilage can also change by metaplasia into fibrous tissue, as is often the case in chronic inflammation of the joints. In the case of hyaline cartilage, fibrous cartilage is sometimes produced as an intermediate stage.

Hyperplasia and Regeneration.—In arthritis deformans and tuberculosis of the joints, hyperplastic proliferation of the cartilage and of the connective tissue may give rise to irregular projections and nodularities,

¹ *Virchow's Archiv*, xxxvii., 212, 1866.² *Berlin. kl. Wochensch.*, 1892.

which are sometimes loosened and form free bodies. Fractures of cartilages—*e. g.*, the costal—heal by the formation of either connective tissue or true bone. In the latter instance the callus is furnished by the perichondrium; the union of divided tracheal cartilaginous rings is accomplished by connective tissue. Mature cartilage-cells have but limited regenerative power. If a bit of cartilage is broken off from an articular surface but little new cartilage is formed, and the defect is filled with connective tissue; the loosened bit may form a free body in the joint-cavity or become fastened again by the proliferation of the synovial membrane.

Perichondritis and Chondritis.—Practically the only place in which inflammation of cartilage assumes an independent position is as costal chondritis. According to the observations of Riedinger, Dittrich, Helferich, and Berg,¹ inflammation of the costal cartilages may be tuberculous or syphilitic; it may also be caused by the bacillus of typhoid fever, the *Micrococcus lanceolatus*, and the *Bacillus coli communis*. The inflammatory changes begin either in consequence of a hematogenous invasion of the perichondrium or due to extension from adjacent tissue. There results more or less thickening of the perichondrium from inflammatory infiltration, followed by its detachment from the cartilage proper. In the cartilage itself there may be multiple foci or cavities, filled with a jelly-like tissue or pus (Fig. 228).



FIG. 228.—Post-typhoid chondritis: *a*, border between the rib and cartilage; *b*, rounded excavations in the cartilage, due to the subperichondral proliferation of granulation-tissue (Berg).

Often the cavities communicate with the external tissue by fine channels, and their formation has been preceded by the growth of vascular granulation-tissue into the cartilage substance. There are also more diffuse necrotic or degenerative changes in the cartilage, which may be abnormally soft or abnormally hard and brittle, showing a yellow discoloration or a marmorated appearance, white and brown. According to Bauer, typhoid chondritis is located on the border, between the cartilage and the bone. From such perichondral and chondral foci may arise parachondral and subcutaneous, as well as subpleural, tuberculous, syphilitic, and nonspecific processes, that communicate with the chondral primary foci by long and tortuous fistulous passages. In chronic cases the perichondrium may become abnormally adherent or the seat of inflammatory osteophytes.

DISEASES OF THE JOINTS.

Hemorrhage.—Hemorrhage into a joint-cavity arises most frequently in consequence of trauma of various kinds, *e. g.*, fractures, sprains, contusions, dislocations; in the hemorrhagic diathesis and in intense joint inflammations

¹ Om reffenskondrit, *Nordiskt Med. Arkiv*, 1895.

hemorrhage also occurs. Hemorrhages from vasomotor disturbances are observed in diseases of the central nervous system. Part of the blood coagulates, and the synovial membrane is covered with coagulum, fluid being absorbed rapidly. The adherent coagula are substituted by new tissue, due to the proliferation of the cells of the synovia, and the free clotted masses may become covered with a layer of flat cells; but subsequently disintegration and absorption take place. The cartilage may become pigmented with yellow and brown spots, in which are found pigment-particles. Fibrous ankylosis may result in occasional severe cases.

Traumatism of the Joints; Healing after Dislocations and Operations; Ankylosis and New Joints.—Traumatism of the joints, as distortions, luxations, subluxations, etc., are immediately followed by hemorrhage into the joint-cavity, and subsequently some inflammatory exudation and infiltration take place. If the dislocated bone-end is brought back into the cavity and retained, and if infection is avoided, then absorption of the blood occurs; the inflammation subsides, and the necessary regenerative changes are initiated; formative tissue is produced, and the fibroblasts heal the

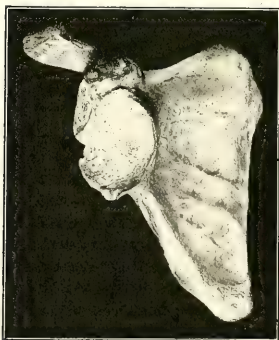


FIG. 229.—New cotyloid cavity developed after unreduced dislocation of the shoulder-joint.



FIG. 230.—Osseous ankylosis of the shoulder-joint in a case of amputation of the forearm, near the elbow.

rent in the capsule and the ligaments, so that the functional capacity of the joint is fully restored; or, in case the traumatism is severe and complicated, the resulting proliferation may lead to more or less adhesive or fibrous arthritis. Should the luxation fail to be replaced, then the capsule and ligaments contract, functionless muscles atrophy, the original joint-cavity becomes obliterated and filled with fibrous tissue, and the cartilage disappears. The dislocated bone-end may become solidly bound to the

tissues about it by new fibrous and osseous tissue, or a new joint-cavity may be formed, which is, in its way, sometimes quite perfect. The constant pressure against an adjacent bony surface—*e. g.*, some part of the scapula or ilium—causes a little depression, around the margins of which the periosteum produces a wall or ring of new bone; a fibrous and in part cartilaginous lining of the new-formed cavity may develop by proliferation and metaplasia of the tissues (Fig. 229). At other times a more or less clumsy bony box is produced.

After resection of a joint the ends of the bones may become united by a fibrous or bony tissue; bony resorption and apposition may in time remodel the ends, which become covered with connective tissue, and a new joint is produced, the lining of which may even secrete a synovial fluid. In the thick and firm connective tissue around and between the ends there may develop more or less hyaline or fibrous cartilage in the young.

Extensive destruction of joint-structure by various forms of disease or by prolonged immobilization may be followed by the consolidation of the joint through the agency of new fibrous tissue, cartilage, or bone. This is known as ankylosis of a joint: true ankylosis, when the fixation of the joints is absolute; false, when some motion exists. Fibrous, cartilaginous, and bony (Fig. 230) describe the nature of the immobilization; of these varieties, the cartilaginous is the most infrequent; often the ankyloses are in part fibrous, in part cartilaginous, etc. Bone-tissue or cartilage may develop in the formative tissue which grows over the joint-surfaces; if the cartilage was destroyed, the exposed bony surfaces stand in the same relation to each other as the ends of a fracture. When the joint-ends are fixed by cicatricial thickening in the capsule, the ankylosis is known as capsular; and when the fixation is due to the contraction of the ligaments and muscles outside of the joint, as extracapsular.

In the young ankylosis is followed by such modifications in the growth of the bones as will produce structural conditions that correspond best to the requirements of the functions; and ankyloses in the old are followed by remodelling of the internal structure of the bone, so as to meet the new static and mechanic conditions; absorption takes place in some places, and growth by apposition in others. In angular ankylosis the bone in the concave part becomes denser, that in the convex more porous.

Spontaneous dislocations occur, in part, in consequence of dilatation of the capsule and stretching of the ligaments by fluid accumulations in the interior of the joint, as in synovitis of tuberculous or other origin; in part, on account of destruction of the bones that enter into the formation of the joint, by suppurative osteomyelitis or tuberculous caries.

Congenital dislocations, oftenest observed in the hip-joint, may depend upon a primary hypoplasia of the joint-cavity, as the acetabulum, so that it remains too small for the head of the femur. Luxation of the hip-joint may be acquired during fetal life, on account of abnormal positions of the lower extremities forcing the head out of the cavity.

For information concerning the congenital and acquired deformities known as club-foot, genu valgum, genu varum, and the spinal curvatures, attention is directed to works on orthopedics.

INFLAMMATION.

In joint inflammations the changes may be confined to the synovial membrane—synovitis—and this is usually the case in acute and beginning inflammations. In the further progress of the process, especially if it be intense, as well as in most chronic inflammations, infiltration and necrosis of the articular cartilages and other joint-structures take place, and the condition then is more commonly and properly referred to as arthritis and periarthritis.

Joint inflammations arise in consequence of traumatism and direct infection, or secondarily to inflammations in the neighborhood, especially in the contiguous bones (osteomyelitis of various kinds). Inflammations of the joints also develop in consequence of hematogenous infection, which may occur secondarily in the course of various infectious diseases, such as pyemia, erysipelas, scarlet fever, gonorrhea, typhoid fever, dysentery, cerebrospinal meningitis, etc., while the synovitis of articular rheumatism is apparently due rather to direct and primary involvement of the joints. It is possible that in this disease toxic substances produce the joint-changes.¹ In acute infectious osteomyelitis the joint infection may arise simultaneously with or secondarily to the bone invasion. Isolated instances of apparently primary hematogenous synovitis also occur. In the secondary forms of hematogenous synovitis the inflammation may be caused by the microbes of the primary disease or by a secondary mixed infection. The so-called gouty arthritis and synovitis are due to the precipitation into the joint-structures of the salts of uric acid. In the chronic, nonspecific forms of arthritis characterized by but little or no inflammatory exudation, the nature and causes are not yet understood (arthritis deformans, neurotic arthropathies).

According to the anatomic characteristics, joint-inflammations are divisible into exudative, dry, and productive varieties. The exudative, which may be acute or chronic, present serous, fibrinous, and purulent as well as mixed forms, depending upon the appearances of the exudate. The dry forms are, in the majority of cases, chronic affections in which other changes than exudation play the more important part. The acute exudative forms are not characterized by definite etiologic relations; the same kind of infection may cause different kinds of exudate. In the metastatic forms the exudate is usually purulent; but the gonococcus causes oftener a serous than a purulent synovitis. In acute articular rheumatism the exudate is oftener serous than fibrinous or purulent.

The Acute and Chronic Exudative Joint Inflammations.—

Serous Synovitis or Arthritis (*Hydrops Articularum*).—In this form the exudate consists of a clear, yellowish, thin fluid, present in varying, often abundant, quantities; the admixture of yellow, delicate, fibrinous flocculi is often noticed. The serous membrane appears more vascular and injected than normal, somewhat swollen, especially in the folds and fringes, with here and there occasional hemorrhagic extravasations; and in acute cases the joint is swollen and the skin over it red. The acute serous synovitis may develop in consequence of slight or severe degrees of traumatism, as sprains and contusions; consequently the exudate in some cases is more or less bloody. It is this form of joint inflammation that, as a rule, accompanies

¹ For a comprehensive discussion of the etiology of acute articular rheumatism, see Packard, *Progressive Medicine*, March, 1900.

acute articular rheumatism in polyarticular distribution, although at times the exudation is more distinctly fibrinous. Serous synovitis often arises as a metastatic inflammation in the course of gonorrhea, with a noticeable tendency to localize in the knee-joint (gonorrheal rheumatism), and undoubtedly in some cases caused by a pure gonococcal infection. The presence of floating bodies in the joint-cavity may give rise to attacks of acute synovitis by causing a certain degree of traumatism of the synovial membrane by being suddenly compressed between the opposing surfaces of the joint. Tumors in the neighborhood also cause joint-exudates, and closed osteomyelitic foci may maintain a recurring serous synovitis.

In many cases of serous synovitis, especially of traumatic origin, there is observed a marked tendency to recidivation and chronicity; in other cases—*e. g.*, those of gonorrheal origin—the inflammation may be chronic from the start. The predisposition of some individuals to synovitis may depend upon an excessive development of synovial folds and fringes, which become compressed during the movements of the joints; in others free bodies may be present.

In the chronic form the amount of exudate may be large; it may be thick or thin; sometimes it is more gelatinous, and contains fibrinous masses; it is always richly albuminous. When the inflammation persists for a long time the synovial membrane becomes thick and opaque, the fringes enlarged, sometimes to such an extent as to form nodular or papillary masses; and the cartilage may become covered with or converted into fibrous tissue, especially around the margins. The overdistention of the ligaments and capsule may allow some degree of spontaneous subluxation of the bone-ends. Not infrequently capsular dilatations in the form of circumscribed hernial pouches occur.

Acute fibrinous or serofibrinous synovitis is characterized by larger fibrinous masses in the exudate, and by the formation of fibrinous layers over the synovial membrane and the articular cartilages; it may occur as a dry, pure, fibrinous form, which is rare. Etiologically it may depend upon acute articular rheumatism and upon various forms of microbial infection, especially with the common pus-cocci. The dry fibrinous form is liable to be followed by chronic changes on account of the substitution of the fibrinous layers with connective tissue, leading to obliteration of the cavity.

Suppurative joint inflammation may be divided into two forms (Volkmann): purulent synovitis, in which the pus is produced by the synovial membrane; and the suppurative panarthrititis, in which all the joint-structures are involved. The purulent synovitis may give rise to diffuse suppurative panarthrititis, or the latter may begin as such. These forms are due to traumatic or hematogenous microbial infection and to extension of suppurative processes, either in the bone, periosteum, or soft tissues.

In the milder form of purulent synovitis the synovial membrane is turbid and thickened, covered with a fibrinopurulent deposit, and microscopically the seat of a marked round-cell infiltration, while the joint-cavity is filled with a purulent, seropurulent, or serofibrinopurulent fluid.

In the more severe form of suppurative panarthrititis the synovial membrane is extensively destroyed, the articular cartilages more or less disintegrated or necrotic, so that the bone-tissue may be exposed, to be followed by osteomyelitis and caries; the joint-capsule and ligaments may be infiltrated and undergo purulent softening, followed by periarticular and

para-articular phlegmonous inflammations or more circumscribed lymphangitic abscesses. When such extensive destructions occur the normal contours of the joints are lost and spontaneous dislocations may take place.

Purulent synovitis from various causes may be followed by more or less perfect recovery ; but, when the process becomes chronic, the cartilages are changed into fibrous tissue and adhesions form, with thickening of the synovial membrane and the capsule, leading to an incomplete, perhaps largely capsular, ankylosis. When the cartilage and bone are involved, true fibrous and bony ankylosis may result after the process is arrested ; periosteal proliferations may cause irregular bone formations about the joint.

Gouty Arthritis (*Gout, Arthritis Uratica, Podagra*).—This form of arthritis is due to the precipitation into the joint-structures of the salts of uric acid (urate of sodium, calcium, magnesium, and ammonium, with carbonates and phosphates of lime, hippuric acid, etc.). In the majority of cases the metatarsophalangeal joint of the big toe is first and principally affected ; but changes may occur in the joints of the hands and fingers, the knee-joint, and elsewhere. The urates are deposited in the form of needle-shaped crystals and granules in the cells and ground substance of the cartilage and in the ligaments, the capsule, the synovial membrane, and the adjacent tissues, followed by hyperemia and inflammatory exudation. The deposition usually takes place intermittently, under the general and local symptoms of an acute attack of gout. According to Ebstein, the unfavorable conditions for intercellular circulation of fluids in the cartilage and other joint-structures lead to arrest of the streams and are followed by circumscribed areas of necrosis, into which the salts are precipitated. Between the attacks of gout the joint-swelling may disappear ; but the articular surface may look as if smeared with plaster of Paris. In aggravated cases the cartilage cleaves asunder and disintegrates, and chronic proliferation and thickening of the synovial membrane and the joint-capsule lead to severe chronic changes. The urates may be deposited in large chalky masses about the joints (*tophi arthritica*), resulting in more or less deformity. Necrosis of the tissues may lead to cavities filled with pus and uratic and necrotic detritus, and perforation of the skin may follow. Urates are also at times simultaneously deposited in various other tissues, such as the skin, subcutaneous tissue, the cartilages of the ears, the eyelids, the kidneys, etc. The underlying condition is the anomalous metabolism of gout.

Chronic Joint Inflammations without Exudation.—Excluding the acute and chronic exudative joint inflammations that nearly always depend upon traumatic, infectious, or toxic causes, the gouty arthritis, and the tuberculous and syphilitic forms, there remain a number of chronic arthropathies, which are not always strictly inflammatory, but often purely retrogressive. They are hard to classify satisfactorily, because the same etiologic factors may give rise to different anatomic changes, and similar anatomic changes may depend upon different causes. In this class belong the diseases of joints due to senile retrogressive disturbances of nutrition, the disease known as chronic deforming arthritis, the changes in the joints that occur in connection with diseases of the central nervous system, and chronic adhesive arthritis, the typical form of which is a chronic polyarticular rheumatic arthritis.

The diseases among which often occur transitional or mixed forms are marked by an absence of, or but little, exudation into the joint-cavities.

Senile arthritis (*arthritis chronica ulcerosa sicca*) begins with retrogressive disturbance of nutrition in the articular cartilages, consisting in fatty degeneration of the cells and a splitting or cleaving asunder of the ground substance, followed by disintegration of the cartilages—hence the term ulcerative—at the points of greatest pressure; gradually extension to all parts of the cartilages occurs, with exposure of the underlying porotic bone, which is then worn away, becoming polished or smooth. In contradistinction to arthritis deformans, there is but little cartilaginous proliferation and ossifying periostitis; but the two conditions are not always readily separated from each other. Kimura¹ places much importance upon atrophy of the bone in this disease. In some cases of senile arthritis the capsule becomes thickened; in others the ligaments become soft. As indicated by the name, the disease occurs in old age, and affects oftenest the hip-joint (*malum coxæ senile*); the head of the femur is deprived of its cartilaginous covering and the bone worn off, so that the normal shape is lost and the neck seems shorter than usual. The disease also occurs in the shoulder-joints and elbow-joints.

Neuropathic Arthropathy.—The changes that take place in connection with certain diseases of the nervous system, especially in locomotor ataxia (Charcot's joints) and in syringomyelia, but also in acute anterior poliomyelitis, compression, degeneration, etc., of the spinal cord, are referred to tropho-neurotic disturbances in nutrition. According to Rotter, the arthropathy of tabes dorsalis involves in 76 per cent. the lower extremities, especially one or both knee-joints; the joint-changes of syringomyelia affect the upper extremities in 92 per cent. of the cases. In the latter instance the location of the joint-changes would correspond to the frequency with which syringomyelia is found in the cervical region of the cord.

The anatomic changes of neuropathic arthropathy correspond, in their lighter degrees, to those of senile arthritis; in the severe forms, to chronic deforming arthritis. It is stated by some authors that the joint-changes of locomotor ataxia are distinguished from those of rheumatoid arthritis by their sudden onset, the increase in the fluid of the joints, the rapid, painless course, and the predominance of destructive changes as compared with productive. The clinical phenomena may differ; the anesthesia, the atactic gait, and the defective equalization of the body-pressure in tabes may increase the destructive changes, but it is not possible to recognize any fundamental anatomic peculiarities of the tabic joint-changes. The destructive changes in the joint-ends may occur rapidly, so that spontaneous luxations and subluxations take place in a short time. Proliferative changes also occur; the bone-ends may become irregularly and greatly broadened, cartilaginous and bony outgrowths appear, free articular bodies are found, and even extensive periarticular productions of new bone. Frequently the rarefaction of the bone is so marked that spontaneous fracture takes place.

Arthritis chronica deformans (*rheumatoid arthritis, arthrite sèche* of the French) is characterized by a combination of proliferative and degenerative processes that result in marked deformities and disfigurement. It may appear as a mono-articular or polyarticular disease. In the first instance it is frequently of traumatic origin, and follows contusions, sprains, fractures, and unreduced dislocations of some larger joints in an otherwise healthy

¹ Ziegler's *Beiträge*, xxvii., 225, 1900.

person. It may be spontaneous. Occasionally a serous or purulent synovitis passes into a deforming arthritis. The polyarticular form, which occurs oftener in women after thirty years of age, involves especially the smaller joints of the hands and feet, but also the larger articulations. The etiology of many mono-articular instances and of the polyarticular varieties is wholly obscure. Preble and the writer observed a well-marked instance in a woman, aged thirty, with multiple fibromas of the nerves. Cases have been described in the young and in children after scarlet fever (Wagner). On the whole, the disease occurs oftenest in older individuals, and is usually associated with arteriosclerosis. The disease is of slow development and chronic course; hence the anatomic changes vary according as it concerns earlier or advanced stages.

The changes in the cartilage consist, according to the investigations of Ziegler, in a splintering of the ground substance, and also in hyaline degeneration, followed by foci of softening and the formation of small cavities. At the same time cartilaginous proliferations form, which give rise to thicken-



FIG. 231.—Arthritis deformans of the hip-joint. The acetabular cavity is larger and deeper than normal, due especially to the high and irregularly thickened rim.

ings, especially at the margins of the articular cartilages. Subsequently ossification may take place. Proliferation also takes place in the joint-capsule, in the ligaments, and in the synovial membrane; the folds and fringes of the latter enlarge, and islands of cartilage, followed by calcification and ossification, develop, and detachment of nodular masses may give rise to loose bodies in the joint. In the meantime the cartilage at the points of greatest pressure during the movements of the joint may be absorbed, and such places are covered again by proliferation of the synovial membrane, or more often the bone is laid wholly bare and assumes a polished, brownish-yellow, glistening appearance, as it is ground down by the articular movements. In addition there occur retrogressive and progressive changes in the adjacent bone, and lacunar absorption removes whole laminae of bone. Kimura emphasizes especially the purely atrophic changes in the bone. The marrow in the subchondral district becomes lymphoid or gelatinoid; islands of connective tissue form, in which new bone may develop by metaplasia; small cysts also form; the subchondral absorption may occur with or without destruction

of the cartilage, and it gives rise to marked deformities of the heads of the various bones, which appear as if flattened out. Concurrent periosteal proliferation produces irregular, rounded, often firm osteophytes, which may form a grotesque garniture around the vanishing bone-ends. In the same manner the acetabular cavity, for instance, becomes widened by the absorption of the old bony margins; but the periosteal proliferation forms a new and higher, thicker and irregular rim (Fig. 231).

In some cases the synovial fat-tissue increases in quantity, perhaps from removal of the normal pressure, and extends into the cavity of the joint in a branching mass, as the so-called *lipoma arborescens*; the detachment of small masses may give rise to another variety of loose joint-bodies. At times the cavity of the joint contains an increased amount of fluid. Ankylosis due to the deformity also occurs, as do luxations.

The combination in varying degrees of these changes produces all kinds of eccentric deformities, the minute description of which is not feasible.

Arthritis deformans oftenest involves the hip-joint, then the knee-, shoulder-, and elbow-joints, the joints of the hands and fingers, feet and toes, and of the spinal column.

In the hip-joint the head of the femur becomes first cylindrical and then mushroom-like (Fig. 232); simultaneously it is depressed and sits directly upon the diaphysis—all due to absorption and peripheral proliferation. The acetabular cavity may be destroyed and a new cavity produced; this may cause shortening of the limb. Sometimes the rim becomes enlarged, so that it grasps the head and prevents its removal from the cavity, and in this way partial ankylosis results.

Arthritis deformans of the spinal column is known as *spondylitis deformans*. Absorption of the anterior parts of the bodies of the vertebræ gives the trunk a forward or stooping position. The margins of the adjacent vertebræ often are united by bony ridges, and irregular marginal outgrowths are common; the bodies seem diminished in size, and the spinal column may become wholly or partly ankylosed in various abnormal positions (Fig. 233).

Chronic Adhesive Arthritis.—In this form of arthritis the articular cartilages are vascularized by proliferation of the subchondral medullary vessels and gradually changed into connective tissue, the synovial mem-



FIG. 232.—Arthritis deformans of the hip-joint. The head of the femur is beginning to assume a mushroom-like shape, due to resorption of the head proper and to proliferation around its periphery.

brane proliferates and covers the articular surfaces, and in this way opposing surfaces are united by fibrous tissue (fibrous ankylosis), which may subsequently become ossified (bony ankylosis). The joint-capsule is thickened and the periarticular tissue sclerotic. At times irregular cartilaginous and osseous proliferations develop, but this is not frequent. Adhesive arthritis may occur as the termination of acute exudative inflammation and of chronic destructive lesions, like tuberculosis of the joints, and it is found in the senile

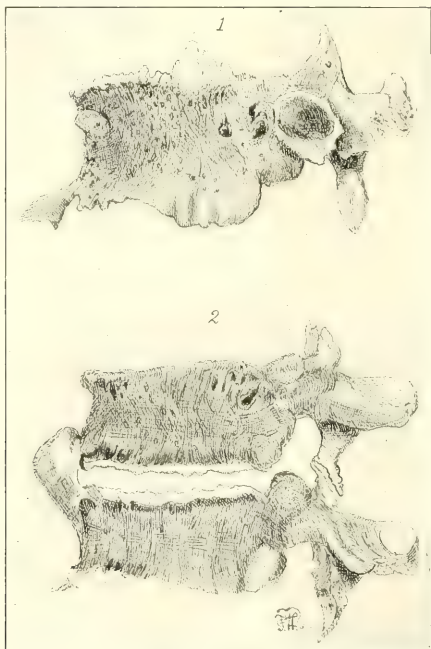


FIG. 233.—Spondylitis deformans: 1, showing the peculiar outgrowths of the margins of the bodies of the costal vertebra, which in (2) has produced a bony ridge holding the two vertebrae together.

joint alterations; or it may develop gradually after acute articular rheumatism or begin more insidiously, in polyarticular form, as a chronic variety of this disease.

Tuberculosis.—Tuberculosis is a frequent joint-disease. It may develop as a clinically primary tuberculosis of the synovial membrane. In this case the hematogenous invasion is secondary to an evident or latent tuberculosis in the lymphatic glands, lungs, or elsewhere, and the primary synovial tuberculosis bears the same relation to tuberculosis in the other organs as bone tuberculosis (page 684).

Joint tuberculosis is more frequently—perhaps in two-thirds of the cases

or more (König, Krause)—secondary to tuberculosis of the bones. The primarily osteal joint tuberculosis is due to the direct extension of the process into the joint from tuberculous foci in bone. Tuberculous foci in the epiphyses of long bones are usually situated so near the articular surface of the joint that on extension the joint-structures become involved; it is also possible that infection of a joint may occur in a more indirect manner through the lymphatics, from adjacent tuberculous bone-areas. It is the frequency of secondary joint invasion that gives osteotuberculosis so much practical importance, as uncomplicated bone tuberculosis is usually symptomless. Slight traumatism plays an evident role in the causation of joint tuberculosis; it appears as the starting point of the disease in 56 per cent. of the cases (Fenger¹). It is thought that the resulting extravasation of blood arrests the tubercle bacilli floating in the circulation, and presents, together with the local injury to the cells, favorable conditions for further development of the germs. It also seems likely that traumatism might hasten the extension of tuberculous bone-foci into the joint. Max Schüller and Krause showed experimentally that a slight traumatism to a joint determines the localization of microbes in the case of animals experimentally infected with tuberculosis.

Formerly tuberculosis of the joints was not recognized as a specific disease, but went under various names, of which white swelling (*tumor albus*) was the most common. In 1844 Rokitsansky stated that miliary tubercles were present in the lesions of white swelling, the process being a tuberculosis of the synovial membrane. This statement passed unnoticed until Virchow and Volkmann again pointed out the presence of miliary tubercles in white swelling, and until Köster, in 1869, positively demonstrated miliary tubercles in all so-called fungous joint diseases. Köster's work was confirmed by Friedländer, Hueter, Billroth, Volkmann, and König; and Volkmann showed the relation of tuberculous joint disease to bone tuberculosis and the great frequency of primary bone-foci. Hueter, Schüller, and others produced the disease experimentally by injections with tuberculous pus, and tuberculosis of the bones and joints had become established as a definite form of disease when Koch, in 1882, placed the question beyond all doubt by showing that the bacillus of tuberculosis is the constant etiologic agent. Krause and others produced bone and joint tuberculosis experimentally by injections with pure cultures of tubercle bacilli.

Tuberculosis of joints is characterized in the main by the same benignancy as bone tuberculosis. The tubercles are composed of epithelioid and giant cells, containing but few lymphoid cells and comparatively few bacilli. During the course of a joint tuberculosis all the constituent parts of the joint may be successively involved, namely, the synovial membrane, the ligaments, and perisynovial tissues, the articular cartilages, and the articular ends of the bones.

The synovial membrane presents more or less distinct grayish and yellowish tubercles, as well as diffuse infiltrations of tuberculous, or so-called fungous, granulation-tissue, characterized by caseous degeneration and softening. At times papillary outgrowths are present; or there forms a thin layer of vascular connective tissue which spreads itself over the articular cartilages like a thin veil, after the manner of a corneal pannus (pannus synovitis). At the same time more or less exudation into the joint-cavity

¹ *Jour. Amer. Med. Assoc.*, 1889.

takes place. The exudate may be serous, serohemorrhagic, serofibrinous, seropurulent, fibrinopurulent, or purely purulent in appearance. When tuberculous granulation-tissue undergoes rapid caseous disintegration and softening, the fluid is like the pus of "cold abscesses," and the condition is in reality a cold abscess of the joint. In some cases tuberculous synovitis may develop without exudation or accumulation of purulent fluid. The destruction of articular ligaments by tuberculous granulation-tissue and the distention of the capsule with fluid within the cavity produce displacements and subluxations. Occasionally so-called rice-bodies (*corpora oryzoidea*) form in tuberculous joints. Rice-bodies are smooth, rather elastic and soft, or gelatinous, of white or grayish-white color, and of varying shape and size; they may be thread-like and branching; usually free, they also appear pedunculated; in structure they present a concentrically lamellated arrangement, and in the larger there may be a central cavity. Rice-bodies are regarded as in part fibrinous formations, in part due to loosened fimbriated and tasselled outgrowths of the synovial membrane that have undergone hyaline degeneration or have been covered with a layer of fibrin. Rice-bodies occur especially in tuberculous joints the seat of serous and serofibrinous exudation; they are rare in the purulent, and still more so in the dry form, of joint tuberculosis. A certain degree of motion in the joint is regarded as necessary for their formation.

In more advanced cases the capsule, the ligaments, and the periarticular tissues become infiltrated with areas of grayish or yellowish granulation-tissue in which are foci of softening.

The number of tubercle bacilli in the fluid and the tuberculous tissue of joint tuberculosis is characteristically small; tuberculosis constantly develops, however, after injection or implantation of material in guinea-pigs and other susceptible animals.

The articular cartilage is usually more or less extensively destroyed and absorbed by leukocytes and cells of the granulation-tissue, which enter it partly from above, partly from below, in their immigration, following, according to Heile, certain preformed paths in the cartilage. The cartilage covering a large sequestrum dies off, and is mechanically detached from the bone in smaller and larger pieces. A tuberculous bone-focus which reaches the cartilage causes a gradual absorption, and one or more local, usually round, defects result, through which granulation-tissue or caseous material protrudes. Tuberculous granulation-tissue in the synovial membrane may extend underneath the margins of the cartilage and gradually dissect it from the bone at the same time as it becomes perforated here and there in a sieve-like manner; finally the whole cartilage, or shreds of it, are found loose in the cavity of the joint. When the tuberculous granulation-tissue spreads over the free surface of the cartilage, the ground substance becomes softened and the cartilage-cells are destroyed. When the joint-cavity is distended with pus the nutrition of the cartilage suffers, and a soft, smeary substance results. In instances of dry synovitis the cartilage may be changed into connective or mucoid tissue.

The bones in the vicinity of the tuberculous joint are usually the seat of osteoporosis. Numerous osteoclasts are situated upon the bony trabeculae in characteristic lacunae. Small bones, like those in the foot, are often so porotic that they are easily penetrated by the probe. When the joint-ends have been wholly or partially deprived of their cartilage, then the bone

substance is gradually destroyed by caries, aided by the mutual pressure which the opposing surfaces exercise upon each other.

In the so-called caries sicca, a thin, rather firm, and relatively avascular layer of granulation-tissue grows, and connects the opposed surface; the cartilage and underlying bone are absorbed, either uniformly or irregularly, so that small and large depressions arise. In this manner extensive defects are produced at the same time as the joint is ankylosed. Dry caries is found most frequently in the shoulder-joint.

In moist, caseating forms, a layer of tuberculous granulation-tissue containing yellow areas covers the bone-ends and extends into the bones for a short distance from the surface. This tissue gradually destroys the bone, so that marked deformities may arise; thus the acetabulum may be widened, and by muscular contraction the head of the femur is brought into abnormal positions within the widened cavity. At other times the floor of the acetabulum is perforated and the head of the femur lies within the bony pelvis. In consequence of extensive destruction, spontaneous luxations and displacements may occur.

Ossifying periostitis near a tuberculous joint may produce flat, irregular, or pointed osteophytes; sclerosis of the bone substance also occurs.

Tuberculous joints are usually swollen; an exception may be found in dry caries. The swelling depends in part upon the increased contents of the joint-cavity, but also upon the changes in the joint-capsule and the periarticular tissues. In the early stages the periarticular tissue is edematous. In the course of the disease chronic productive changes occur in the capsule, the ligaments, and the periarticular connective tissue; adjacent tendon-sheaths may be obliterated. Tuberculous granulation-tissue may infiltrate the tissue outside of the joint, either by direct extension through or rupture of the capsule, or by way of lymphatics. Caseation and softening may result in cold abscesses, that tend to extend indefinitely in the direction of least resistance. The communication of extra-articular foci with the joint may be through tortuous fistulous passages; external perforation may occur. According to combinations, in varying but usually quite characteristic manner and degree, of proliferative, exudative, and destructive changes, tuberculosis of the joints is usually divided into the following anatomic forms:

1. **Acute miliary synovial tuberculosis** is characterized by numerous miliary tubercles upon the synovial membrane, without marked inflammatory changes. It develops in the course of acute general miliary tuberculosis. Occasionally it is associated with cold abscesses of the joint.

2. **Pannous Tuberculous Synovitis.**—The synovial membrane is but slightly thickened, and the tubercles may or may not be large enough to be seen with the naked eye. A thin, vascular layer of granulation-tissue creeps over the surface of the cartilages, which gradually are transformed into connective tissue.

3. **Diffuse Granulomatous Synovial Tuberculosis.**—In this form the synovial membrane is the seat of more or less thickening from infiltration with tuberculous tissue, in which visible tubercles are present. It is usually accompanied by invasion of the para-articular tissues and the ligaments of the joint, and there is formed thick, gelatinous masses of tissue, which contain areas of dry caseous matter or multiple tuberculous abscesses. This form, without much accumulation of puruloid fluid in the cavity, represents the most common variety of articular tuberculosis. The extension of the

infiltration toward and into the subcutaneous tissue renders the skin whitish and immovable and gives the swollen joint the appearance from which the time-honored name of white swelling is derived.

In the dry or atrophic variety of diffuse tuberculosis (*caries sicca* of Volkmann) there is a distinct tendency on the part of the tuberculous tissue to cicatrization, accompanied with caries of the bones and obliteration of the joint-cavity. It is most frequently observed in the shoulder-joint, and is usually a primary synovial tuberculosis.



FIG. 234.—Papillomatous hyperplastic tuberculous synovitis of the knee-joint. There existed a moderate accumulation of serous fluid in the joint-cavity. The synovial membrane is everywhere covered with papillomatous villous masses of varying size, in which are areas of tuberculous granulation-tissue.

4. The Tuberos or Nodular Forms of Tuberculous Synovitis (Fig. 234).—In this form subsynovial tuberculous masses of fibrous structure infiltrated with miliary tubercles and larger caseous areas of varying size, often larger than a walnut, protrude into the joint-cavity; the surface of the synovial membrane is either normal or the seat of a serous or pannous synovitis. In other cases the hyperplastic tuberculosis is more diffuse, the whole surface of the synovial sac being covered with sessile and pedunculated papillomatous and branching growths, small and rather uniform in size, some of which may be detached and form rice-bodies. Microscopically the growths consist mostly of fibrous tissue, covered with fibrinous layers and containing tubercles and caseous areas, sometimes also islands of fat-tissue, and representing then perhaps cases of synovial tuberculosis developing in arborescent lipomas of the synovial membrane.

5. **Tuberculous Hydrops** (König).—Diffuse synovial tuberculosis, with but little thickening of the capsule, is commonly associated with accumulation of clear or milky, serous or serofibrinous fluid in the joint-cavity. Similar accumulations may form also in the nodular, and more rarely in the diffuse, varieties. Rice-bodies may be present, derived from fibrinous material or from detached papillomatous growths.

6. **Tuberculous Empyema or Cold Abscess of Joints**.—The internal surface of the joint is covered with a loosely adherent tuberculous membrane, similar to that of cold abscesses elsewhere, and easily scraped away. The remaining synovial membrane is diffusely infiltrated with tuberculous tissue, but there is no invasion of the para-articular structures. The cavity of the joint is filled with "tuberculous pus."

Tuberculous infection of the regional lymphatic glands occasionally occurs in joint tuberculosis.

Tuberculosis of a joint may be practically the only tuberculous focus in the body. Customarily it is associated with latent or active tuberculosis in other organs, especially the lungs and the lymphatic glands, as well as bones and other joints. Under such circumstances chronic or acute general miliary tuberculosis or tuberculous leptomeningitis not seldom develops. General miliary tuberculosis may develop after operation upon tuberculous joints, but traumatic dissemination of tubercle bacilli probably does not occur as often as was formerly believed. Amyloid degeneration may develop after continued articular tuberculosis. Tuberculosis of joints may heal, with more or less perfect motion in the affected articulation. Usually, however, there remains some thickening of the capsular and periarticular tissues that prevents free motion and causes deformity. When there has been destruction of the articular cartilages and of the bone-ends, adhesive arthritis, with fibrous or perhaps bony ankylosis in more or less abnormal positions, may terminate the process. Articular as well as osseous tuberculous foci may remain latent for years, and healing may be more apparent than real. Ankylosis in abnormal positions may change the normal directions of the mutual pressure of bone-ends, and in young persons this sometimes results in excessive growth in length (or elongation), as in the knee-joint, where the lower femoral epiphysis may grow excessively in cases of permanent flexion. It is more common for excentric atrophy or osteoporosis to occur in the bones in joint tuberculosis, especially when the disease necessitates permanent rest in bed or a prolonged disuse of the extremity. In such cases the cancellous bone becomes porotic, the compact layer greatly thinned, and the amount of fatty marrow increased. Such bones break easily. The atrophy is succeeded by a restitutive growth by apposition as soon as the normal functional activity is resumed. In young persons the protracted inactivity is followed by a diminished growth in size (hypoplasia) of all parts of the extremity; this must be distinguished from complete arrest of growth in length of a single bone, *e. g.*, the femur, that occurs when the intermediary cartilage is destroyed by the disease. The destruction of synchondroses by tuberculosis may lead to premature synostoses.

Syphilis.—In hereditary syphilis, a primary exudative arthritis, with fibrous thickening of the joint-capsule and ulcerative disintegration of the cartilages, sometimes occurs (Hueter); gummatous inflammation in neighboring tissues may secondarily invade a joint; sometimes congenital syphilitic osteochondritis leads to epiphyseolysis and consecutive articular inflammation.

In acquired syphilis serous forms of synovitis occur during the period of eruption, more particularly in the sternoclavicular joint. In the late periods of the disease, chronic arthritis, sometimes polyarticular, is described (Virchow). This rare articular affection is characterized by gummatous foci in the synovial membrane, the capsule, and the intra-articular periosteum. On healing, characteristic irregular and radiating depressions, with precise serrated margins, smooth floors, and at times partly filled with a radiating cicatricial tissue, are produced; sometimes the scars are confluent and the joint-surfaces irregularly nodular; here and there islands of cartilage remain.

Actinomycosis.—Metastatic actinomycosis of the joints has been described in a few cases. In Petroff's case one elbow-joint was involved; in Orloff's, the tibiotarsal. In a case of generalized actinomycosis following a probable primary cervico-oral localization, described by J. Müller, a double actinomycotic coxitis, with spontaneous dislocation, occurred. In O'Neil's and Mallory's cases there were abscesses over the metacarpal joints.

In cases like these, metastatic foci are also encountered in the skeletal muscles and in the intermuscular tissue (Köhler).

Joints are also invaded by extension, as, for instance, the articulations of the cervical vertebræ, when prevertebral actinomycosis attacks the spine and the base of the brain; the sternoclavicular joints in thoracic processes; and the hip-joints in the limitless extension of abdominal actinomycosis.

TUMORS OF THE JOINTS.

Joints are frequently invaded by tumors originating in adjacent bone. It is rare that tumors develop primarily in joints. Sarcoma may develop in the capsule of joints. Proliferation of fat-tissue in the synovial layers may give rise to the so-called lipoma arborescens, in which the joint-recesses are filled by papilliform branching fat-masses. Lipoma arborescens is rather frequently observed in the joints already affected with tuberculosis or arthritis deformans.

Echinococcus-cysts of the joints occasionally occur, and are nearly always secondary either to cysts in bone or in adjacent muscles.

FLOATING BODIES IN THE JOINTS.

Loose bodies in the joints arise in various ways, and occur in previously healthy and in previously diseased articulations.

1. Loose bodies arising in previously healthy joints frequently consist of cartilage or cartilage and bone; isolated examples of loose foreign bodies and changed blood-clots occur. The essential cause of this group is traumatism, in consequence of which variously shaped bits of cartilage and bone become detached. According to Schüller, the injury may result from forced movements, either in normal or abnormal directions, or from external forces acting directly upon the articular surfaces or their cartilaginous margins. Such bodies remain partially adherent or they are completely detached, either at once or by subsequent changes. It has been shown by Barth and Schmitt that the cartilage of loose pieces may maintain its vitality for a long time, and even proliferate and produce new bone. Of 85 traumatic cases collected by Schüller, 78 were of the knee, 5 of the elbow, and 2 of the wrist. Loose joint-bodies, or joint-mice, produce sudden locking of the

joint, especially the knee, by becoming arrested between the anterior surfaces of the bones and the capsular ligaments; they also lead to recurring serous synovitis that may produce more or less thickening of the ligaments and the capsule.

As explaining the development of loose bodies not directly caused by traumatism, König described a peculiar inflammatory condition, in consequence of which small pieces of the articular ends of bones are loosened; this process König named *osteocondritis dissecans*, and Paget "quiet necrosis." The process may follow traumatism or originate spontaneously; but its exact pathogenesis is not understood, and its existence is denied by Barth, who refers floating bodies of obscure origin either to unrecognized traumatism or to *arthritis deformans*. Riedel and others, however, describe cases in which articular cartilage of the head of the humerus is said to have been detached by *osteocondritis dissecans*.

2. Loose bodies arising in diseased joints consist of various formations, such as, to mention the more frequent, the rice-bodies of exudative tuberculous arthritis, which are partly fibrinous concretions and partly detached and degenerated synovial fringes and villi; detached or pedunculated sub-synovial papillomatous fatty masses in the condition known as *lipoma arborescens* of joints; and finally, the cartilaginous proliferations of articular cartilages and in synovial villi of *arthritis deformans*. In the last case increase in the size may occur from actual proliferation of the cells of the cartilage, nourishment being supplied by the synovial fluid, and from depositions of fibrinous layers upon the exterior. Calcification commonly occurs in the center.

VOLUNTARY MUSCLES, TENDONS, TENDON-SHEATHS, AND BURSÆ.

THE VOLUNTARY MUSCLES.

THE essential elements of the voluntary muscles are the striped muscle-fibers. The fibers are cylindric, about 4 to 5 cm. in length, varying in diameter from 10 to 50 μ , and possessing a regular transverse striation due to various discoid elements which make up the contractile substance of the individual cylinders. Each fiber is enclosed in a clear, elastic, structureless membrane—the sarcolemma. Beneath this, on the surface of the contractile substance, lie the nuclei, elliptic in shape, and placed with their long axes parallel to the long axis of the fiber. The contractile substance possesses a characteristic and complicated structure. It is made up of ultimate fibrillæ, which microscopically appear as fine light or dark longitudinal striations.

The muscle-fibers are aggregated into small groups, these into bundles, and these again into larger fasciculi, which in turn form the parts of an anatomic muscle. Around the larger bundles lies a sheath of connective tissue—perimysium; from this minute layers extend into the bundles and surround the individual fibers—endomysium. The voluntary muscles are richly supplied with blood-vessels, the arteries and veins being situated in the perimysium and the network of capillaries in the endomysium around the individual fibers. The capillaries anastomose freely with each other. The nerve terminations of voluntary muscle are exceedingly complicated in structure.

Congenital Malformations and Anomalies.—These are not rare, and are frequently found in dissection and at autopsy. Supernumerary bundles or anomalous distribution of bundles are of most frequent occurrence. There may be also a failure of development of certain muscles or groups of muscles. More rarely there may be a development of muscles corresponding to certain muscles in the lower animals. These may be looked upon as atavistic reversions.

Circulatory Disturbances.—Circulatory disturbances of the muscles for the greater part disappear entirely after death or are recognized with great difficulty. Only the grosser changes, as hemorrhages or large areas of anemic necrosis, stand out prominently.

Anemia.—This may be part of a local or general anemia. The former may be caused by arteriosclerosis, obstruction of the arteries, or by local compression. The muscle is pale and softer than normal. In general anemia the muscles are paler and dryer than normal; but the paleness may be covered up by an increase of pigment which gives to the muscle a brown color.

Hyperemia.—Congestive hyperemia may be seen in the neighborhood of

inflammatory conditions. It usually entirely disappears a short time after death. Passive hyperemia rarely occurs except in cases of extreme vascular stasis.

Edema.—In general edema the intermuscular connective tissue may show an extreme degree of edema—even dripping on section. Lighter grades are shown by increased moisture and decreased consistency. Chronic edema may lead to hydropic degeneration. The presence of edema in muscles is shown microscopically by the appearance of small clear vacuoles throughout the protoplasm. These may become confluent in severe cases, and the muscle-fiber may eventually undergo liquefaction.

Hemorrhages.—These may be large, small, or punctate. The first are usually of traumatic origin, and may occur in healthy muscle; they may also result from rupture caused by convulsive contractions—tetanus; or in consequence of increased blood-pressure. The hemorrhage may be preceded by local degenerative changes in the vessel-walls or in the surrounding muscle, as in typhoid or typhus fever, sepsis, pernicious anemia, etc.; in the neighborhood of inflammatory processes; or the extravasation may have its origin in contiguous structures. In typhoid fever the hemorrhage occurs most frequently into the muscles of the abdominal wall—*hematoma recti abdominis*. Small punctate hemorrhages are of frequent occurrence in the acute infections, phosphorus poisoning, leukemia, and pernicious anemia.

The muscle-fibers are pushed apart by the blood or destroyed if the extravasation is large, the muscle substance undergoing liquefaction or coagulation necrosis and mingling with the blood-products. Organization and absorption of the blood-clot soon take place, resulting in the formation of a pigmented scar in which regeneration forms of muscle-fibers are found. These for the greater part undergo atrophy or necrosis, so that the number of new fibers persisting is very small.

Infarction of Muscle.—The rich collateral circulation and free anastomosis of the vessels supplying muscle do not favor its necrosis or degeneration as a result of thrombosis or embolism of its main vessels. But in cachectic conditions, fevers, etc., in which the nutrition of the muscle is already lowered, an anemic necrosis may result from arteriosclerosis, deficient heart action, local compression, infiltrations, etc. Such anemic infarctions are seen in senile gangrene, decubitus, etc. In embolism of the vessels of the muscles abscesses may result if the emboli are infective, as in malignant endocarditis, pyemia, etc.

Psoas Infarcts.—Total anemic necrosis of the psoas may occur as a result of long-continued recumbent position, as in chronic pulmonary tuberculosis, paralysis, etc. It is usually associated with bed-sores. The main arteries of the muscle may contain obliterating thrombi or may show a proliferating endarteritis. Hemorrhages occur in the sheath and intermuscular septa, especially about the nerve-trunks. The entire muscle may undergo a Zenker's necrosis, appearing like fish-flesh, white and translucent; but usually small hemorrhages are scattered throughout the connective tissue. When only a portion of the muscle is involved, the necrosed anemic areas may be surrounded by extensive extravasations. If the necrosed area becomes infected, a primary psoas abscess may result. In other cases the dead muscle is replaced by scar-tissue in which attempts at muscle regeneration may be found. The left psoas is more frequently involved than the right.

Retrogressive Changes.—**Atrophy.**—The size of a muscle is deter-

mined by the functional demands made upon it. An increase in the amount of its work leads to an hypertrophy in case the muscle does not become fatigued. If fatigue ensues, atrophy accompanied by degenerative changes results. If the function is lessened or entirely suppressed, the muscle likewise undergoes atrophy. The diminution of function may be due to inactivity, to general nutritional changes, to changes in the muscles themselves, or to diseased conditions in the spinal cord or peripheral nerves. Several forms of muscular atrophy may therefore be recognized which present clinically distinct characteristics.

Simple Atrophy.—This is the most common form ; it occurs regularly in old age—senile atrophy—and in all wasting and cachectic conditions, as tuberculosis, carcinoma, etc. In this class also belongs the atrophy resulting from disuse—lack of exercise, joint disease, etc.—from compression by tumors, inflammatory exudates, etc. Overwork, continued contraction as in tetanus, stretching of the muscle by the growth of a tumor between or beneath the bundles, local or general anemia, widespread arteriosclerosis, weakened heart action, general lowering of nutrition, intoxications : all have

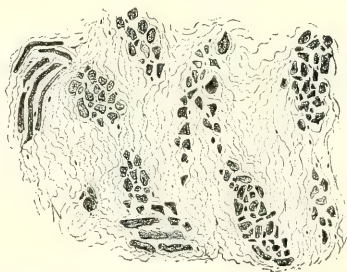


FIG. 235.—Atrophy of the skeletal muscle following degeneration of the ganglion-cells of the anterior horns of the spinal cord. $\times 175$.

a deleterious effect upon the muscles and lead to atrophy and degeneration. The factors of pressure, disturbance of circulation, nutrition, and function take part in these changes.

Atrophic muscles may appear pale or like fish-flesh ; or brown, from an increased production of muscle-pigment—brown or pigment-atrophy. The atrophic muscle is usually dryer and firmer than normal ; but it may appear moist and colloid-like in serous atrophy. Microscopically the fibers appear reduced in size without any marked change in the contractile substance. The fibers gradually become thinner, and at last wholly vanish. The striations are preserved until a certain thinness is reached. The atrophic fibers may contain no pigment, or there may be present fine granules of a yellow or brown pigment—hemofuscin. In rare cases a hydropic degeneration of the fibers may take place—serous atrophy. There is usually an increase of the intermuscular connective tissue, with more or less formation of adipose tissue replacing the vanished muscle—*atrophia lipomatosa*.

A pure, simple atrophy occurs, as a rule, only in the senile cases. In those forms dependent upon inflammatory conditions, new growths, poor nutrition, intoxications, infections, fatigue, etc., the atrophy is usually asso-

ciated with degenerative changes, such as cloudy swelling, hydropic and fatty degeneration, fragmentation, lacunar erosion, or Zenker's necrosis.

Neuropathic Atrophy.—In the group of muscle-atrophies that are classed as neuropathic the cause lies in a diseased condition of the peripheral or central nervous system. The muscle-atrophy of spinal origin arises as a result of the degeneration of the motor cells of the anterior horns and medulla. The pyramidal tracts are usually involved. In some cases the degeneration has been traced to the motor cells of the motor cortex. The condition is known as progressive spinal muscular atrophy. Closely allied to it are the diseases known as amyotrophic lateral sclerosis and progressive bulbar paralysis. The anatomic basis is a slow atrophic change in the motor nuclei.

The typical form begins usually in healthy and strong individuals, and, as a rule, in those muscles which are most frequently used. In hand-laborers the muscles of the ball of the thumb and little finger, the interossei and the lumbricales, are first affected. Sometimes the disease begins in the

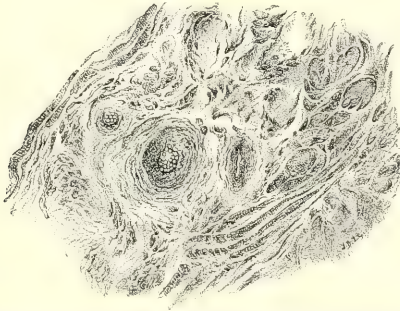


FIG. 236.—Neuropathic muscular atrophy, showing atrophy of the muscle-fibers, increase in the inter-fascicular fibrous tissue, and thickening of the blood-vessel walls (Stengel).

arm- and shoulder-muscles. From the muscles first affected the disease spreads slowly to other muscles or muscle-groups, usually involving them symmetrically, but sometimes in irregular succession. In the severest forms all of the muscles of the body may be affected. In many cases the disease comes to a standstill after a number of muscle-groups are involved. The muscles of the lower extremities are usually attacked late. There are, however, atypical forms which begin in the lower extremities and gradually extend to the upper.

The atrophic muscles are pale, colorless, or brown; and flabby in consistency. The fibers of single muscles may disappear entirely, so that only the connective tissue remains. Here is usually a fatty infiltration. The large vessels show thickened walls, and in many cases a proliferating endarteritis leading to obliteration. A proliferation of the connective tissue occurs to some extent; also a limited regeneration of the muscle. The regenerating fibers show various degenerative changes. The muscle-fibers disappear either by simple atrophy or there may be degenerative changes, as cloudy swelling, fatty degeneration, longitudinal or transverse fragmentation, etc.

Secondary neuropathic or neurogenous atrophies of muscle occur in various spinal diseases—syringomyelia, tabes dorsalis; and as a result of injuries or degeneration of motor nerves, neuritis, lead poisoning, and of degenerations following cerebral disease. The muscle-changes are similar to those in spinal atrophy, but the clinical picture is different.

Myopathic Progressive Muscular Atrophy¹ (*Primary Myopathy, Dys-trophia Muscularis Progressiva*).—This form of muscle-atrophy is a primary disease of the muscle; no changes are found in nerves or cord. Its etiology is not yet known, but it is probable that some congenital anomaly of development lies behind it. It is frequently hereditary. Three clinical forms—infantile, juvenile, and adult—are recognized. There are also forms named according to the localization of the affection. The infantile form may develop in earliest childhood, and affects most frequently the muscles of the face. In severe cases a stupid, mask-like expression—myopathic—is produced. The juvenile form affects the calves, thighs, back, shoulders, and arms. The adult form may begin in the buttocks, thighs, or calves, or in the shoulder- and face-muscles.

Anatomically there are two forms, the simple atrophic and the pseudohypertrophic. The microscopic picture of the former may be similar to that of the neuropathic form, but there is usually presented a combination of changes. The fibers may be partly atrophic, and in part may show a true hypertrophy. The hypertrophy may precede the atrophy. Fragmentation and vacuolation are common. There may be a reactive proliferation of the endomysium.

The pseudohypertrophic form is characterized by a marked formation of adipose tissue. The cells of the endomysium undergo an active proliferation and become changed into fat-tissue. This may occur to such an extent that the muscle not only does not lose its size, but may also become greatly increased in bulk, producing the appearance of a muscle-hypertrophy. The lipomatosis is either the primary change causing the atrophy of the muscle-fibers, or it follows the disappearance of the muscle; or the two processes may go on together. In the majority of cases it is evident that the formation of fat-tissue follows the atrophy; but in certain cases the fatty infiltration of the endomysium is the primary change. The muscle-fibers are pushed apart by the fat and undergo a secondary degeneration.

The most marked cases of the pseudohypertrophic form occur in children, especially in boys. Several members of the same family may be affected and the condition may be inherited. It affects chiefly the muscles of the calves, thighs, buttocks, and shoulders; the hands and arms, as a rule, are not involved.

Degenerations.—Cloudy Swelling (*Granular or Parenchymatous Degeneration*).—The muscle-fibers are swollen, the striations are indistinct or have entirely disappeared, and the protoplasm appears more granular than normal. In the freshly teased specimen these granules dissolve in acetic acid. In hardened specimens the swollen fibers stain more deeply than usual with hematoxylin. The degeneration occurs as a result of high temperature, intoxications, disturbances of circulation, inflammations, etc. It is frequently associated with fatty degeneration, or may precede it.

Hydropic Degeneration (*Vacuolar Degeneration*).—A partial liquefaction

¹ Erb, Leipzig, 1891; Strümpell, *Zeitschr. f. Nervenheilkunde*, 1893; Roth, *Ziegler's Beiträge*, 1893.

of the muscle-protoplasm leads to the formation of clear vacuoles throughout the fiber. The fresh muscle thus affected appears pale and watery. The degeneration occurs in suppurative inflammation, or as a result of chronic edema, etc. It may be distinguished microscopically from simple edema of the muscle in that in the degeneration the muscle-nuclei do not stain well, while in simple edema they do. It must, however, be borne in mind that edema leads ultimately to hydropic degeneration.

Fatty Changes.—The protoplasm of the muscle-fibers may undergo a fatty change whereby numerous small droplets of fat appear throughout the contractile substance. These may become confluent into large drops. The muscle-fibers appear hazy, lighter, do not stain so well with eosin, and the nuclei usually show degenerative changes. The fresh muscle has a yellowish color, tears easily, and in advanced cases may have a fatty sheen. The fat-droplets are always more plainly seen in the freshly teased specimen or after treatment with osmic acid. The degeneration occurs in extreme degree in phosphorus poisoning; to a less degree in fevers, intoxications, cachexias, tuberculosis, etc.

Necrosis.—**Simple necrosis** of the muscle-fibers occurs in inflammations, fevers, intoxications, near malignant growths, etc. The fibers appear swollen, without nuclei, and show no striations. They stain deep bluish red with hematoxylin and eosin.

Liquefaction necrosis of the muscles occurs in suppurative inflammations and as a result of chronic edema.

Coagulation Necrosis (*Zenker's Necrosis*¹).—The waxy or hyaline necrosis, first described by Zenker as occurring in typhoid fever, consists of a homogeneous or hyaline change in the contractile substance whereby it becomes swollen, loses its striations, and finally breaks up into small hyaline masses, which gradually become absorbed. As a rule, the hyaline substance takes none of the ordinary stains; sometimes it stains as fibrin with the Weigert fibrin-stain, in other cases as colloid with Van Gieson's and other stains. When the degeneration affects single fibers it is not visible to the naked eye; but if of wide extent the affected muscle appears white, translucent like fish-flesh, and of soft consistency. As a result of this softening large hemorrhages may occur, as the hematoma of the abdominal wall in typhoid fever. The psoas, abdominal muscles, and the adductors of the thigh most frequently show this form of necrosis.

It occurs in all severe fevers, intoxications, particularly in typhoid, acute tuberculosis, sepsis, variola; also in wounds, inflammations, anemic necrosis, decubitus, burns, freezing, forced muscle contractions, as in tetanus, near carcinoma, etc. In severe cases the muscle-nuclei are completely destroyed; in lighter cases they may recover and lead to entire or partial regeneration of the fiber. Associated with or following the degeneration there is usually a small-cell infiltration of the endomysium. Forced contraction of muscle affected with the degeneration leads to hemorrhage.

Gangrene.—This occurs in senile gangrene, decubitus, severe infective inflammations, burns, freezing, and as a result of lowered nutrition of the skin and subcutaneous tissue in places exposed to pressure. The muscles become brownish black or greenish in color, break up into shreds, or liquefy. If exposed to the air the evaporation of the part may result in mummifica-

¹ Zenker, *Ueber d. Veränderung. d. willkürlichen Muskeln bei Typhus Abdominalis*, Leipzig, 1864.

tion. Microscopically the fibers show a simple liquefaction or coagulation necrosis; the fibers entirely lose their form; there is a marked small-cell infiltration; blood-pigment, cholesterol, triple-phosphate crystals, etc., may be found in the débris. Putrefactive germs are present. Large vacuoles from the formation of gas-bubbles may be found in the tissue. In mummification the cells shrink, gradually losing their form, and at the same time their nuclei, until at last a horn-like substance is produced.

Fragmentation; Fibrillation.—Not infrequently in necrosis the muscle-fibers break up into longitudinal fibrillæ or into transverse masses which either appear normal or cloudy or hyaline. This change is usually associated with hydropic or Zenker's degeneration, and occurs in infections, inflammations, etc.

Bleb-like Degeneration.—Hoen¹ has described a peculiar form of degeneration of the striped muscle of the uvula, characterized by a bleb-like change, associated with pigment formation and nuclear proliferation.

Fatty Infiltration.—Fat is deposited in the connective-tissue cells of the endomysium in atrophic conditions of the muscles (see Atrophy). A proliferation of the connective-tissue cells may precede the deposit of the fat, which may be either primary or secondary to the atrophy of the muscle.

Amyloid Degeneration.—The formation of amyloid in muscle is rare and only of local occurrence, especially in the muscles of the tongue and larynx. In these muscles the amyloid may form large nodular masses. The deposit begins in the capillary walls of the endomysium, and may extend around the sarcolemma, causing an atrophy of the fiber. The atrophic fiber appears as if surrounded by a glassy hyaline substance. Ultimately the fiber disappears, and the confluence of the deposits leads to the formation of nodular masses.

Calcification.—This occurs most often in the intermuscular scar-tissue resulting from inflammatory processes or about old abscesses. The muscle-fibers themselves may undergo calcification in severe atrophy, and as a sequel to fatty change.

Pigmentation.—An increase of the muscle-pigment occurs in atrophic conditions. This pigment, which is called hemofuscin, appears in the form of minute yellow or brownish granules which are usually arranged at the poles of the muscle-nuclei. The chemical nature of this pigment is not known, but it is probably a product of the muscle-protoplasm. An increase of it is therefore to be regarded as a degeneration rather than a deposit.

Hemosiderin and hematoïdin may be found in the scars of recent hemorrhages. The pigment may persist for a long time, but is gradually removed.

Hypertrophy and Regeneration.—A true hypertrophy of the muscle-fibers occurs but rarely, and is usually the result of excessive use. The individual fibers are increased both in length and thickness, and there is also most probably an increase in the number of the fibers. Hypertrophy of certain muscle-groups occurs in various forms of labor (laborers' hypertrophy). In very rare cases congenital hypertrophy may occur. In the spinal form of progressive muscular atrophy single fibers of the atrophic muscles may show an increase of size. It is very probable that this enlargement is degenerative in character. A true muscle-hypertrophy has been observed after typhoid fever, and injuries may lead to localized hypertrophy.

¹ *Journal of Experimental Medicine*, iii., 549-572, 1898.

In the rare disease *myotonia congenita* (*Thomsen's disease*) Erb¹ found in excised pieces that the muscle-fibers were doubled in size, with increase of their nuclei and a loss of striation with vacuolation of the muscle-protoplasm. These changes he considered to be of the nature of a true hypertrophy, but they are more probably degenerative. The compensatory hypertrophy of the diaphragm in chronic disturbances of respiration may lead to such enlargement of its crura as to produce pressure furrows in the liver.

Regeneration.—The degree and character of the regeneration of voluntary muscle depend essentially upon the nature of the injury to the muscle. Only in slight lesions of the contractile substance when the sarcolemma and muscle-nuclei are preserved is a perfect regeneration possible. This may occur after freezing or after the degenerative changes of typhoid fever, sepsis, and in very slight traumatic injuries in which but little of the muscle substance is lost. The destroyed portion of the fiber is replaced by a new

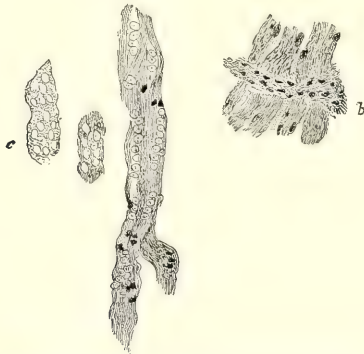


FIG. 237.—Regeneration of striated muscle: a, cell in muscle-bud in mitotic division; b, scar-tissue between divided fibers; c, giant-cell-like masses. $\times 250$.

growth proceeding from the muscle-nuclei and sarcoplasm yet remaining in the sarcolemma. This regeneration repeats perfectly the embryonal type of muscle formation.²

In more severe injuries (trauma, operation, etc.) regeneration of muscle-fibers takes place only in a limited degree, the destroyed muscle being replaced by a granulation-tissue arising from the intramuscular connective tissue. After the lapse of several weeks new muscle-fibers may be found penetrating into the granulation-tissue. These new fibers arise through direct and mitotic division of the neighboring muscle-nuclei, in whose fibers there is a new formation of protoplasm, so that from the ends or body of the old fiber protoplasmic offshoots are thrown out. These buds possess no striations, are rich in large nuclei, and on section appear as large epithelioid cells. The sarcoplasm of the old fiber passes without a break into that of the offshoot. Later there is a differentiation of the new sarcoplasm into new fibrillæ, which possess at first a longitudinal and later a transverse striation (Fig. 237). From one muscle-bud several new fibers may be formed. The

¹ *Die Thomsen'sche krankheit*, Leipzig, 1886. ² Volkmann, *Ziegler's Beitrüge*, xii., 1892.

active proliferation of the neighboring muscle-nuclei leads also to the formation of free wandering cells, which by growth and division form epithelioid giant cells. The majority of these undergo a fatty degeneration or necrosis; some unite with old fibers or with the protoplasmic buds, while others may form new muscle-fibers. The separation of the nerve-supply of the muscle does not interfere with the process of regeneration, but in many intense inflammatory processes unfavorable conditions of nutrition may result in a complete absence of regenerative-effort.

Inflammation (*Myositis*).—The inflammatory conditions of the muscles are most often secondary to those of neighboring structures or are traumatic in origin. They may also arise from the presence of micro-organisms or poisons in the blood, or from disturbances of nutrition. The secondary forms of myositis arise by extension from inflammation of bones, joints, skin, mucous membranes, pleura, peritoneum, perirenal tissues, etc. (phlegmon, decubitus, etc.). The hematogenous forms of myositis occur in pyemia, infective osteomyelitis, puerperal pyemia, malignant endocarditis, typhoid fever, trichinosis, actinomycosis, glanders, anthrax, acute rheumatism, etc. According to the nature of the process, a number of forms may be recognized.

Acute Parenchymatous Myositis.—This process partakes more of the nature of a degeneration than of an inflammation. Microscopically the chief changes are found in the muscle-fibers, which may show cloudy swelling, fatty or hydropic degeneration, Zenker's necrosis, fragmentation, etc. The capillaries of the endomysium are congested, and the intramuscular connective tissue is edematous with increase in the number of wandering cells. The process is usually a transitory one, and recovery may take place without marked changes in the muscle if destruction of the fibers does not occur. It occurs most frequently in typhoid fever, as a result of slight injuries (bruising and stretching), disturbances of circulation, in spinal and myopathic atrophy, near hemorrhages, and in the neighborhood of new growths. It is of very frequent occurrence in the pectoral muscles in cancer of the breast, even in muscle-bundles at some distance from the invading growth. It is also found in the neighborhood of encysted trichinae, anthrax-pustules, in phosphorus poisoning, etc.

Primary Acute Polymyositis.—A peculiar form of acute myositis has been described by Wagner,¹ Strümpell, and others. It is characterized clinically by fever, painful swellings of the muscles of the extremities and back and of the tongue. The remaining muscles of deglutition and those of respiration are very rarely involved. There is usually a complete loss of voluntary motion of the affected muscles, and slight pressure is painful. A widespread edema of the skin and subcutaneous tissue is also present, and may be so great as to cover up the swelling of the muscles. Associated with the edema is a diffuse hyperemia of the skin, and exanthemas of various kinds may occur. For this reason the disease has been termed dermatomyositis. Since the clinical picture greatly resembles that of trichinosis, it has been mistaken for that condition, and the name pseudotrichinosis² has been suggested for it. Mild cases may recover, but the disease is usually fatal, terminating after several weeks or even months in pneumonia, etc.

Nothing is known of its etiology, but its infectious nature can hardly be doubted. Microscopically the muscle-fibers show cloudy swelling, coagula-

¹ *Arch. f. kl. Med.*, xl., 1887.

² Hepp, *Berl. klin. Wochenschr.*, 1887.

tion necrosis, loss of striation, with proliferation of the muscle-nuclei, and small-cell infiltration of the endomysium.

Acute Interstitial Myositis (*Productive Myositis*).—This is almost always secondary in its origin, and may arise under greatly varying conditions. The primary change is in the connective tissue, which undergoes an active proliferation leading to a secondary degeneration of the muscle-fibers. These may remain unaltered for a long time, and in light cases may even undergo a true hypertrophy. The disease is usually slowly progressive in character and passes into the chronic form. The lighter grades occur in typhoid fever, chronic irritation, as a result of frequent hypodermic injections, severe rheumatism, spinal and muscular atrophy, etc.

Acute Purulent Myositis (*Purulent Myositis*).—The purulent form of myositis is the result of an infection which may be either hematogenous or secondary; and is in its character dependent upon the nature of the infective agent, the location and condition of the muscle in which it occurs. The secondary form is most common. It is usually diffuse or phlegmonous in character, and arises from infected wounds, skin-phlegmons, erysipelas, puru-

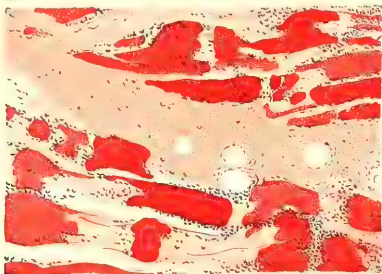


FIG. 238.—Acute hemorrhagic purulent myositis; hematoxylin and eosin. $\times 175$.

lent arthritis, decubitus, etc. The affected muscle becomes mottled yellow, brown, red, and greenish in color, swollen, and softened. The pus may burrow along the sheaths of the muscle-bundles to a distance from the seat of the inflammation. The hematogenous form (pyemia, malignant endocarditis, glanders, etc.) occurs in the form of single or multiple small circumscribed abscesses scattered throughout the muscle in the shape of yellowish softened areas. Microscopically these consist of small cavities filled with pus and tissue-débris, the surrounding muscle being edematous and presenting various stages of degeneration (Fig. 238). A microscopic examination of the pus should always be made, otherwise the abscesses of glanders, etc., may be mistaken for more common purulent processes.

The phlegmonous form very frequently becomes gangrenous in character, whereby the affected muscle becomes greenish or black, disintegrates, and undergoes partial liquefaction (decubitus, etc.). When exposed to the air gangrenous muscle very quickly evaporates (mummification). Small abscesses may be absorbed or encapsulated; larger ones may heal after the discharge of the pus, and a scar results, which in time contracts and may be partly replaced by newly formed muscle-fibers. Lime salts may be deposited in

the scar-tissue. If encapsulation of the abscess occurs without evacuation of its contents, these may undergo liquefaction and a cyst be formed, or calcification may occur.

Chronic Myositis (*Fibrous Myositis*).—A chronic interstitial myositis occurs in spinal and myopathic atrophy, in the neighborhood of chronic inflammations of bones and joints, chronic skin-ulcers, chronic eczema, chronic pleuritis, chronic lymphadenitis, near parasites, foreign bodies, etc. As a result of the hyperplasia of the intramuscular connective tissue fibrous bands may be formed throughout the muscle, or the entire muscle may come to consist of a fibrous membrane.

Chronic Purulent Myositis.—Chronic muscle-abscesses may follow acute infections with pyogenic organisms, but are usually caused by tuberculosis, actinomycosis, glanders, etc. The abscess is surrounded by a membrane of granulation-tissue. They occur most frequently in the psoas-muscle.

Myositis Ossificans.—Under varying pathologic conditions there may occur in the intermuscular and intramuscular connective tissue, as well as in the tendons, fascia, and ligaments, a formation of new bone. In the majority of cases this takes place after the manner of periosteal bone formation; only in rare cases is cartilage formed. Under the influence of extrinsic or intrinsic causes the connective tissue of the muscles undergoes a marked proliferation, forming masses of granulation-tissue which encroach upon the neighboring muscle-fibers. These remain unaltered or undergo degenerative changes, or actively proliferate, forming new muscle-cells, which for the greater part degenerate. At a certain stage in the development of the granulation-tissue, it may suffer a direct change into myxomatous or osteoid tissue, or true bone. Two distinct clinical forms may be recognized, and it is probable that the pathologic conditions underlying these are different.¹

Traumatic Myositis Ossificans.—The traumatic form arises after chronic irritations, overwork, chronic inflammations, etc.; but may follow acute myositis. In some cases the formation of bone seems to follow very slight and acute injuries, or may appear to arise spontaneously. Thrombosis of the femoral vessels and their branches may also be followed by the formation of bone in the surrounding connective tissue. The muscles most frequently affected are the deltoid and pectoral (drill-bone), thigh-adductors (riders' bone²), arm- and leg-muscles (gymnasts' and dancers' bone). The newly formed bone may be in the shape of irregular masses, plates, splinters, nodules, etc.; these may become attached to neighboring bones, forming fixed exostoses, or may remain unattached as movable masses in the muscles.

Progressive Myositis Ossificans.—This is a disease of early life, but may begin later. It is of a slowly progressive nature and lasts many years. The bone formation begins, as a rule, in the muscles of the neck, back, or thorax, and spreads thence gradually over the entire body. Frequently there are multiple seats of origin. The formation of the bone is usually preceded by painful swellings of the affected muscles. The process may advance continuously or there may be periods of rest. The character of the bony growth may vary greatly in different parts of the body, flat plates, irregular nodules, splinters, etc., being formed. In some cases the perimysium is chiefly affected; in others the fascia and tendons. The spinal column and the joints may become ankylosed; muscular movements are

¹ Cahen, *Deut. Zeitschr. f. Chir.*, xxxi., 1890.

² Schmitt, *Rev. de Chir.*, x., 1890.

gradually restricted and at length lost entirely, so that finally the individual may come to be a mass of ossification incapable of motion.

Practically nothing is known of the etiology of this disease. It has been thought to have some connection with syphilis and with certain diseases of the spinal cord (tabes, syringomyelia). The formation of splint-bones in the muscles of the extremities after excessive use may be looked upon as an atavistic reversion. The connective tissues of the muscles may be regarded as of the nature of a skeletal framework, and the formation of bone in this as an expression of a bone-forming diathesis. Through congenital or fetal disturbances or trauma the osteogenetic tissue of the periosteum may have been displaced into the muscles; or osteoblasts may have wandered from the periosteum into the muscle, so that sharp lines between the latter and the connective tissue no longer exist. In this way the intermuscular connective tissue may have acquired a periosteal character. The association of microdactylism in about 75 per cent. of the cases has been taken as favoring the theory of congenital disturbances.¹ Some authors regard the bone formation to be of the nature of a neoplasm, and include the process with the osteomas. The nature of the growths, however, differs in many respects from that of the true neoplasms.

Tuberculosis.—Primary tuberculosis of the muscles is rare. Hematogenous infection may occur in general acute miliary tuberculosis;² or in rare cases miliary tubercles may arise in the muscles independently of any other focus of infection. As a result of this primary infection, diffuse masses of granulation-tissue resembling sarcoma may be formed. These may caseate or heal, being replaced by scar-tissue, which not infrequently becomes calcified. In other cases the confluence of caseating nodules leads to the formation of a cold abscess, whose cavity is lined with a granulation-tissue membrane in which tubercle bacilli are found.

The secondary tuberculosis of muscles is relatively common. It is usually the result of an extension of a tuberculous process from neighboring affected bones, joints, skin (lupus), mucous or serous membranes. The intramuscular connective tissue becomes thickened; in it caseating tubercles develop, through the confluence of which cold abscesses are formed. These are found most frequently in the muscles of the spinal column, pelyis, and hip-joint. In tuberculous caries of the lumbar vertebræ and pelvic bones the iliopsoas is very commonly involved, cold abscesses being formed, which may extend under Poupart's ligament into the muscles of the thigh and discharge through fistulous openings. It must be borne in mind, however, that not all primary psoas-abscesses are tuberculous in nature.

Syphilis.—The most common syphilitic affection of the muscles is a chronic interstitial inflammation.³ The biceps and the muscles of the neck are usually involved. As a result of the great increase of the muscular connective tissue and the secondary atrophy of the muscle-fibers severe contractures may be produced. Gummas are of relatively frequent occurrence in the connective tissue of the muscles, especially in the biceps, muscles of the neck, back, tongue, and the sphincter ani, where they may form large tumors which gradually encroach more and more upon their surroundings, and finally

¹ Nicolaysen, *Norsk Magazin for Lægevidenskaben*, 1899; Boks, *Berl. klin. Wochenschr.*, 1897; Lydia De Witt, *Amer. Jour. Med. Sci.*, cxx., 295, 1900.

² Lanz u. de Quervain, *Arch. f. kl. Chir.*, xlv., 1893.

³ Neumann, *Vierteljahrsch. f. Derm. u. Syph.*, xv., 1888; Leconi, *Charité annalen*, 1891.

caseate, forming deep ulcers or abscesses. These usually heal readily, forming large and deep scars which may interfere very much with muscular movements. An interstitial myositis usually accompanies the development of the gummas. Microscopically the latter consist in their earlier stages of nodules of granulation-tissue rich in blood-vessels, and greatly resemble sarcomas, for which they may be mistaken. The older gummas show the characteristic three zones: A central one of caseation, an intermediate one of mature fibrous tissue, and an outer one of granulation-tissue containing many blood-vessels. Giant cells may or may not be present. The richness of blood-supply and the absence of tubercle bacilli are the distinguishing points from tuberculosis.

Actinomycosis.—An infection of muscle with ray-fungi can occur either through metastasis or as a direct extension from some neighboring primary focus, as in the pleura. Nodules of granulation-tissue are formed, which have a tendency to undergo a fatty degeneration and suppuration. These may slowly heal or abscesses may result. Healed foci are hard to distinguish from syphilitic myositis.

Glanders.—A lymphogenous or hematogenous infection of muscle may occur, leading to the formation of multiple miliary abscesses throughout the muscle. These have a dirty grayish color, and contain a thin, greasy fluid, in which the presence of the bacilli of glanders may be demonstrated by staining with methylene-blue. Extensive suppurative infiltration of the muscle may result. The process may become chronic, resulting in chronic ulceration or abscess. The calf-muscles are most frequently involved.

Tumors.—Primary tumors arising from the muscle-fibers are very rare; usually the new growths of muscle take their origin from the intermuscular connective tissue, the fascia, ligaments, etc. It has been claimed that the muscle-fibers may undergo a sarcomatous change, but the evidence of this is very slight.

Sarcoma.—This is by far the most common tumor of the muscles, and takes its origin from the connective tissue. Very large tumors may occur. They are usually soft and cellular, of the round- or spindle-cell type, and are not infrequently myxomatous in parts. Fibrosarcoma, myxosarcoma, and liposarcoma are among the forms commonly found. The arrangement of the sarcoma-cells often suggests that of muscle-bundles. Not infrequently there is a metaplasia into bone or cartilage. Retrograde changes are frequent. The new growth extends chiefly by expansion, but also by infiltration, causing atrophy and necrosis of the surrounding muscle. The sarcoma-cells may penetrate through the sarcolemma into the substance of the muscle-fiber, and so give rise to the impression that they arise directly from the muscle-fiber. Rhabdomyosarcoma and rhabdomyoma have been observed in a few instances in the shape of small solitary nodules. It is probable that they arise from embryonic inclusions, and not from the muscle-fibers of the region, though the latter origin cannot be disproved. Secondary sarcoma from the bone and periosteum may invade the muscles.

Mature Connective-tissue Tumors.—The connective-tissue tumors—fibroma, chondroma, and osteoma—are rare. Hard fibromas occur in the fascia of the recti abdominis. The formation of bone in myositis ossificans (page 734) differs in many ways from the true tumors. The cavernous angioma is of relatively frequent occurrence; lipomas, angioliipomas, and myxomas are not rare. Myxoma is found most frequently in the thigh-muscles, and is very likely to become sarcomatous.

Carcinoma.—This occurs in muscle as a secondary growth only, usually as a direct infiltration or lymphogenous metastasis from some neighboring primary carcinoma, as that of the breast, lips, and skin. Hematogenous metastasis of carcinoma into muscle is not common. The muscle-secondaries of cancer do not usually attain a great size, but appear either as a diffuse infiltration or in rows of miliary nodules. The muscle-fibers take no active part in the growth, but suffer marked degenerative changes and deformities from the pressure of the new growth. Often an appearance similar to the lacunæ of Howship is formed in the sarcolemma by the pressure of the tumor-cells against the membrane. An invasion of the contractile substance through a rupture of the sarcolemma may occur. Simple atrophy, coagulation and liquefaction necrosis are very common in the muscle-fibers in the neighborhood of an infiltrating carcinoma. The fibers at a distance from the tumor or surrounding inflammation may show these changes, thereby suggesting the presence of toxic substances in the tissues. The muscle near an invading carcinoma shows always a more or less severe interstitial myositis, and the neighboring blood-vessels an obliterating vasculitis.

Teratoma.—Small teratomas and dermoid cysts are sometimes found embedded in the muscles of the cheek, root of tongue, neck, lumbar region, and abdominal wall. They represent, as a rule, monogerminal inclusions, but may arise from a bigerminal implantation. In the abdominal recti small adenomas or cystadenomas (enterocysts) may occur rarely as the result of the inclusion of a portion of the omphalomesenteric duct (umbilical adenoma).

Animal Parasites.—The *Trichina spiralis* is the most important of the muscle-parasites. It occurs in the muscles in its encysted stage of development (measle); and is found in greatest numbers in the diaphragm, tongue, intercostal muscles, muscles of the neck, larynx, and thighs, and is more sparsely scattered in the remaining muscles of the trunk and extremities. The measles are most numerous, as a rule, near the tendons. The embryos are developed in the intestine, and penetrate thence through the lymphatics into the muscles. Here the worm invades the muscle-fibers, destroying their contents. The affected fibrillæ appear swollen, lose their striations, and contain granular masses which stain deeply with eosin. In the beginning the parasite is surrounded by the dilated sarcolemma alone. Between the coils of the worm there is a fine granular mass. Later a clear, hyaline, chitin-like capsule is formed about the parasite. The muscle-nuclei undergo active proliferation, and in the intermuscular connective tissue there is a small-cell infiltration with fibroblastic proliferation. In this inflammatory area are found large numbers of eosinophiles¹ and plasma-cells. After some time the acute inflammatory changes disappear and the capsule becomes infiltrated with lime salts. The calcified capsules appear to the naked eye as small whitish spots; by transmitted



FIG. 239.—*Trichina spiralis* encysted in muscle; teased fresh specimen.

¹ Brown, *The Journal of Experimental Medicine*, iii., 315, 1899.

light they appear cloudy and opaque. The parasite may live in the calcified capsule for an indefinite time, even to the death of the individual.

Cysticercus Cellulosæ.—This parasite is occasionally found in the muscles, forming cysts surrounded by a thick fibrous capsule of the size of a bean or pea. From the pressure of the surrounding muscle-fibers the cyst usually assumes a spindle shape. Only one parasite may be found, though usually several are scattered throughout the muscle. If cysticerci are found in the brain, the muscles should always be carefully searched. Their presence excites a slight local myositis.

Echinococcus.—This occurs as a very rare parasite of human muscle. It is found most frequently in the muscles of the inner sides of the extremities. The parasite becomes encysted and may live for many years. Lime salts are deposited in the capsule.

THE TENDONS, TENDON-SHEATHS, AND BURSÆ.

The tendons consist of bundles or fascicles of a peculiar firm connective tissue, which contains no blood-vessels. Each fascicle is made up of ultimate bundles of fibers, which are arranged in parallel rows, between which lie the tendon-cells. Between and around the fascicles lies a looser connective tissue, containing blood-vessels, binding the fascicles together and continuous with an outer covering of similar tissue, which invests the entire collection of fascicles forming the tendon. This plays freely in a synovial cavity formed by the tendon-sheath, a membrane surrounding the tendon, but wholly or almost wholly separated from it. The surface of the sheath is kept moist by a scanty synovial secretion.

The structure of the primary bundles, possessing as they do no blood-vessels, does not favor the origin of primary pathologic conditions; and the morbid changes which are found in them are usually secondary to neighboring processes. Primary changes, however, may arise in the interfascicular connective tissue. The tendon-sheaths, being similar in structure to the synovial membrane of the joints, may be affected by similar pathologic processes to those found in the latter. There are, however, a number of conditions peculiar to tendon-sheaths or to these in common with the bursæ.

Circulatory Disturbances.—As a result of trauma large hemorrhages into the cavity of the tendon-sheaths may occur, forming a hematoma.

Retrograde Changes.—Atrophy.—In progressive atrophy of the muscle the tendon and tendon-sheaths usually persist unchanged for a long time after the complete disappearance of the muscle; gradually they undergo atrophic changes associated with an infiltration of fat between the bundles. The latter may retain their outline, even when no trace of muscle is left, but frequently they become fused into flat bands of scar-like connective tissue in which the characteristic arrangement of the tendon-cells is lost. This change may be preceded by a fibroblastic proliferation of the interfascicular connective tissue.

Necrosis and degeneration of the tendon-bundles may occur in severe inflammatory processes. *Mucous degeneration* of the sheath and interfascicular tissue is also frequent in inflammation. *Colloid-like bodies* may be formed upon the surface of the sheath or in the cavity of the sheath in chronic inflammatory processes. *Hyaline bodies*, the so-called corpuscula

oryzoidea (rice-bodies), are frequent accompaniments of chronic inflammation and tuberculosis of the sheath (see below).

Hyaline change and calcification are frequent accompaniments or sequelæ of chronic tendinitis and tendovaginitis. *Amyloid deposit* has been stated to occur in the walls of the interfascicular blood-vessels, but this occurrence is very rare or doubtful. *Urates* are deposited in the connective tissue of the tendon and upon the surface of the sheath in certain cases of gout.

Pigmentation.—*Hemosiderin* may be found in large quantity in the interfascicular tissue after hemorrhages. As a consequence, the affected tendon may be of a light or deep chocolate-brown color. The tendons and tendon-sheaths of old individuals often show a diffuse pigmentation, sometimes granular, the nature of which is not known. Under the term *ochronosis*, a brownish or black pigmentation of cartilage, tendons, tendon-sheaths, and synovial membranes has been described. The nature of the pigment, which contains no iron, has not yet been made out. It is supposed to be an imbibition of a diffuse iron-free blood-pigment, and is probably closely allied to the pigmentation of old age.

Regeneration of Tendon.—In severed tendons that are not infected the ends are united by connective tissue which is more like scar-tissue, less glistening and more grayish in color than the tendon. Definite bundles are not formed, but the new-formed tissue fills up also the interfascicular spaces. The process must be looked upon as of the nature of a functional regeneration. Both the tendon-cells and the cells of the interfascicular tissue take part in this regeneration, but the greater part of the new tissue comes from the latter.¹

Metaplasia.—Here may be mentioned the metaplasia of tendon and tendon-sheath into myxomatous tissue, cartilage, or bone, which may occur as a sequel of chronic inflammatory conditions.

Inflammation.—The most common and important pathologic conditions of the tendons and tendon-sheaths are inflammatory in character. There is a close analogy to the inflammations of the joints both in regard to etiology and the character of the process. They are for the greater part traumatic, more rarely secondary to neighboring inflammations, and still more seldom primary in origin.

Tendinitis.—Wounds, bruises, stretching, tearing, etc., may lead to an inflammation of the interfascicular tissue of the tendon-bundles. The exudate may be serous, fibrinous, or purulent in character. In the latter case the tendon-sheath is usually involved, and the infection is the result of extension from the neighboring tissues. As a result of the purulent infiltration of the tendon, necrosis and liquefaction of the tendon-bundles may occur. A primary hematogenous tendinitis² may also arise from the presence of gonococci, pus-cocci, or pneumococci in the blood. The gonorrheal form is relatively frequent. It may be confined to the tendon alone or involve it in common with the tendon-sheath. It may be serous, fibrinous, or purulent in character.

An idiopathic tendinitis (the so-called rheumatic inflammation) is also of relatively frequent occurrence. The tendons of the extremities are most often involved, especially the Achilles, and the extensor tendons of the forearm. It may occur as a result of overexercise, violent stretching of the

¹ Viering, "Reg. d. Sehnengewebes," *Virchow's Archiv*, cxxv., 1891.

² Garré, *Beiträge zur klinische Chirurgie*, viii., 1891.

tendons, or of persistence in certain athletic sports or forms of labor, or following exposure to damp and cold. In many individuals it is apparently associated with climatic conditions, and is closely allied to the gouty diathesis. The tendon-sheath is almost always affected. There is usually but little serous exudate, a slight fibrinous deposit being formed over the surface of the tendon and tendon-sheath, which gives rise to a friction-crepitus.

Primary tendinitis may also occur very rarely as a complication in the course of the acute infections, scarlatina, typhoid, etc.

Chronic tendinitis is usually associated with chronic tendovaginitis, but may exist without changes in the sheath. It may follow an acute tendinitis. Partial destruction of the tendon-bundles may result. The interfascicular connective tissue becomes increased in amount, and may undergo a hyaline change or calcification. In other cases a myxomatous tissue is formed between the bundles; or a metaplasia into bone, cartilage, or adipose tissue may take place. In certain forms of rheumatism (*rheumatismus nodosus*) nodules of granulation-tissue from the size of a pin-head to that of a bean may be formed in the interfascicular tissue. Usually after two to three months these disappear entirely, or a few may persist as hyaline bodies, which ultimately may undergo calcification. Also in gout (see below) chronic changes with deposit of urates may occur in the interfascicular tissue.

Partial regeneration of destroyed tendon-bundles may occur in chronic tendinitis.

Tendovaginitis (*Tendosynovitis*, *Tenosynovitis*, *Thecitis*).—The involvement of the tendon-sheath alone, or of both sheath and tendon, are the most common and important pathologic conditions affecting these structures. The inflammation usually begins in the sheath and extends thence to the tendon. According to the nature of the inflammation we may distinguish:

Acute Dry Tendovaginitis.—This form is characterized by a deposit of fibrin upon the surface of the sheath, with little or no serous exudate. The friction of the roughened surfaces in movements of the tendon gives rise to a crepitus, which may be easily felt by the hand, or even heard at some distance from the patient. It occurs most frequently in the Achilles after excessive walking or jumping, exposure, etc., but may be idiopathic (rheumatic). Next in frequency it occurs in the extensor tendons of the forearm as the result of persistence in certain forms of hand-labor.

Acute Purulent Tendovaginitis.—The purulent form arises most often from injury to the part, or as an extension of purulent inflammations from neighboring structures, as infected wounds, phlegmons, abscesses, panaritides. It may have a hematogenous origin from the presence of gonococci, pus cocci, or pneumococci in the blood. It is characterized by a purulent exudate, which collects in the cavity of the tendon-sheath. The interfascicular tissue is edematous and contains an abundant small-cell infiltration; its blood-vessels are congested. As the process advances the tendon-bundles become cloudy and swollen, suppuration of the interfascicular tissue takes place, the ultimate fibers become separated, and a liquefaction of part or all of the tendon may result. If healing takes place without necrosis, adhesions between the tendon and its sheath may be formed; also scar-tissue between the bundles, in which calcification may occur later. Regeneration of the destroyed tendons may take place.

Chronic Tendovaginitis.—A dry and a serous form may occur. The latter is not uncommon. The exudate is serous in character, containing

mucin or pseudomucin. It may cause a great distention of the tendon-sheath (*hydrops, hygroma*). Chronic irritation may lead to the occurrence of fluid accumulations in the sheaths without other marked inflammatory changes. The dilatation may be so great as to partake of the nature of a cyst formation. This occurs most frequently in the palm of the hand and in the sheaths of the flexors of the hand. The cyst is usually constricted at the point where the tendons pass under the annular ligament, so that the tumor may have an hour-glass form or the appearance of a sacculated growth.

In rarer cases the tendon-sheaths of the fingers, back of the hand, and other muscles may suffer a similar change. Through hydropic distention of inflammatory diverticula of the tendon-sheaths arises the so-called ganglion, a cyst with colloid or mucous contents. The true ganglion of the fingers has a different origin (see below). In time the wall of the hygroma becomes thickened, calcification may occur, papillary or villous growths may arise in the wall, consisting of granulation-tissue, which later may become hyaline or calcified, or even change into cartilage, bone, or myxomatous tissue. The inner wall of the cyst may be covered with a fibrinous exudate, which may become partly organized, forming hyaline masses or bodies containing few cells. These partially organized masses of fibrin, when villous or polypoid in shape, may become loosened from their attachments and appear as free bodies, the so-called rice-bodies (see below).

Gout.¹—Urates may be deposited into the interfascicular tissue of the tendons. Associated with this deposit or secondary to it there is a necrosis, followed by inflammation and proliferation of the interfascicular connective tissue. The fascicles may be pushed apart by the formation of a granulation-tissue which is rich in cells; it may contain giant cells and deposits of urates. The sheaths may become involved in this process and incrustated with a layer of crystals of uric-acid salts (*tendinitis* and *tendovaginitis proliferata urica*).

Gonorrhea.—Jacoby and Goldman² found gonococci in the tendon-tissues in acute suppurative tendovaginitis.

Tuberculosis.—This may be secondary to tuberculosis of the joints or bones, or primary. The tubercles develop in the wall of the tendon-sheath. Their growth is usually accompanied by exudative processes. Polypoid or fungous masses of epithelioid tissue may be formed in the walls, their surfaces covered with fibrin or pus. The fluid portion of the exudate may be scanty or in great abundance, forming a hygroma. A chronic inflammation with hydrops formation is almost always tuberculous in nature. Rice-bodies (see below) are commonly present in large numbers. The wall of the sheath becomes nodular or diffusely thickened by masses of tubercles and by hyperplasia of its connective tissue. Primary tuberculosis of tendon and tendon-sheath occurs most frequently in the forearm.³

Syphilis.⁴—But little attention has been paid to the syphilitic affections of the tendons and tendon-sheaths. They are usually confounded with tuberculosis, which they much resemble both in the clinical symptoms as well as in the histologic changes. It is, however, probable that syphilis of the tendons is much more common than primary tuberculosis. *Tendovagin-*

¹ Berkart, *British Medical Journal*, 1895.

² *Beiträge zur klinische Chirurgie*, xii., 1894.

³ Schuchardt, *Virchow's Archiv*, cxxxv., 1894.

⁴ Schuchardt, *loc. cit.*

itis acuta syphilitica occurs in the secondary stage. It does not differ in character from the nonsyphilitic inflammation. Syphilitic hydrops is more common in women than in men, and affects usually the extensors of the fingers and toes, the biceps, and peroneus. A gummatous tendinitis also appears to be not infrequent. It occurs usually in the Achilles and in the tendon of the radialis. The histologic changes do not admit of a differential diagnosis between tuberculosis and syphilis. The history of the case, the bacteriologic investigation, and the therapeutic test must be relied upon for this.

Corpuscula Oryzoidea (*Rice-bodies, Melon-seed-bodies*).—These little bodies that to the naked eye resemble rice-grains or boiled sago-grains consist of a hyaline substance, which is either homogeneous, granular, or arranged in layers, in which nuclei are not present or are found in very small numbers. In the central portion of the body there is usually a small cleft. Many possess a definite capsule, which is narrow, consisting of concentrically arranged layers, which may contain few or many nuclei. Others consist of a fibrous tissue, which in parts contains nuclei, and in other parts shows hyaline change with disappearance of the nuclei. Some consist



FIG. 240.—Portion of a rice-body from a tendon-sheath. The body shows a peripheral zone containing nuclei, but is for the greater part composed of closely set, irregular hyaline masses. $\times 60$. (After Kibbert.)

entirely of fibrin which is becoming organized and hyaline. In others bands of fibrin may be found throughout the fibrous tissue or in the hyaline mass. Giant cells and collections of leukocytes may be found in some, and frequently tubercle bacilli are present in the mass, but usually in greater numbers on the surface.

The reaction of these bodies to stains varies in different cases. Many stain like fibrin with Weigert's fibrin-method, but the hyaline substance is not fibrin in the majority of cases. Usually it stains a deep red with Van Gieson's method; these cases do not give the fibrin reaction. In other cases Van Gieson's method gives a yellowish or brownish stain, and the hyaline substance in these cases may or may not stain as fibrin. Others stain diffusely blue with hematoxylin, showing the presence of lime salts.

As indicated by the staining, the nature and genesis of these bodies must vary. They may consist of fibrinous masses that were deposited upon the inner surface of the tendon-sheath or bursæ and afterward became loosened; or of fibrinous masses that have become either wholly or partially organized and afterward loosened; or they may arise from loosened masses of tuberculous or syphilitic granulation-tissue. This last mode of origin is probably the most common. The wall of the sheath consists of an infil-

trated granulation-tissue containing tubercles and giant cells. On the inner surface of the granulation-tissue there are formed polypoid or villous masses that have a tendency to undergo a hyaline or colloid-like change. Over the whole lies a thick exudate of fibrin. The connective tissue of the papillæ proliferates into the fibrin, organizing it and gradually undergoing change into a hyaline substance devoid of nuclei. In this manner there are formed at the end of the papillæ firmly attached hyaline bodies, which later may be set free as rice-bodies. Around the loosened body a fresh deposit of fibrin may occur, and through its organization or hyaline change the body may acquire a concentric appearance. The hyaline change may begin in the center of the body or at the periphery, or may form masses or bands throughout the body. Similar processes are seen in the healing of peritoneal tubercles and in the organization of fibrinous exudates elsewhere.

There has been much dispute over the origin of the fibrin in these bodies, some observers claiming that it is due to a "fibrinoid degeneration" of the



FIG. 241.—Polypoid granulations on the inner surface of a synovial bursa. The tissue is partly poor in cells, and partly rich in them, corresponding to the course of the vessels. The dark areas are hyalin. (After Ribbert.)

granulation-tissue. This view receives no support from the actual facts in the case, which plainly show that it is of exudative origin.

Tumors.—**Sarcoma, myxoma, osteoma, and chondroma** may develop in the connective tissue of the tendon or its sheath. A rare growth of the tendon-sheath is the *lipoma arborescens*,¹ which consists of multiple branched papillæ of adipose tissue.

BURSÆ.

The bursæ are connective-tissue membranes that enclose small cavities containing a small amount of a clear synovial fluid. The inner surface of the membrane is similar to that of the tendon-sheaths and the synovial membranes of the joints. They are found where muscles or tendons play over bony parts or where the skin, muscles, or fascia is subjected to pressure or friction. The location, number, and size of these structures vary greatly with the individual; many are not constant in appearance, and others may be acquired by various forms of occupation, exercise, etc., and may develop in regions that normally contain no bursæ. Their structure being similar

¹ Haeckel, "Lipoma Arborescens," *Centralblatt f. Chir.*, 1888.

in all respects to that of the tendon-sheaths, their pathology is practically the same as that of the latter. The inflammatory and tuberculous conditions are the most common and important.

Bursal Hematoma.—The normal bursal sac as well as that of a hygroma may become distended with blood as a result of hemorrhage into the cavity following trauma or disturbances of circulation. Coagulation and organization of the blood-tumor may take place, and a firm mass, of the nature of a hard fibroma, result. This may later undergo calcification.

Bursitis.—Acute inflammation of the bursæ arises most frequently after contusions, wounds, etc. Rarely it is of hematogenous origin from the presence in the blood of pus-cocci, gonococci, or pneumococci. The exudate is most frequently serous, giving rise to the formation of an acute hygroma. Serofibrinous and purulent exudates also occur, and may cause great distention of the bursal sac. The purulent inflammations are almost always the result of extension from neighboring inflammations.

Chronic bursitis appears most often in the form of a *hydrops* or *hygroma bursarum*, which arises from the distention of old or newly formed bursæ. It occurs most often in the prepatellar bursa (housemaids' knee), or in the bursæ at the elbow-joint (miners' elbow). The hygroma is usually of the size of an apple, but may become much larger, forming a large fluctuating tumor. The cavity of the hygroma is usually sharply outlined by a connective-tissue wall, which may be thin and delicate or thick. It may undergo calcification, or a metaplasia into bone or cartilage may take place. The inner surface may be smooth, or covered with dendritic papillæ that

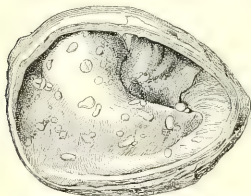


FIG. 242.—Prepatellar synovial bursa cut obliquely and spread out, showing rice-bodies both free and embedded (Ziegler).

may become cartilaginous or myxomatous. Free bodies, sometimes of masses of cartilage of the size of a chestnut, may be found in the cavity, similar to those found in the cavity of the joints. If the exudate is fibrinous in character, numerous rice-bodies may be formed. Their presence is usually to be taken as evidence of the tuberculous nature of the case. The contents of the hygroma are usually thick, mucous, or colloid-like, at first containing much albumin and mucin; but later they become thinner and more serous in character. In gout

deposits of urates may be found on the bursal sheath.

Ganglion Crepitans.—Occasionally the bursal sac becomes filled with rice-bodies, so that pressure upon the tumor gives rise to a peculiar crepitus. Such a cyst has been termed ganglion crepitans.

True Ganglion.—The so-called ganglion of the wrist, back of the hand and foot, was formerly considered to be either a hydrops of the tendon-sheaths combined with changes in the overlying skin, or to be distended diverticula of tendon-sheaths or bursæ. These were thought to be analogous to the hernia-like protrusions of synovial membranes of the joints. According to Ledderhose,¹ true ganglion is a new formation, and not the result of pathologic changes in either bursæ or tendon-sheaths. There first appear small areas of myxomatous tissue in the para-articular connective tissue, which increase in size and become confluent. This mucous tissue

¹ *Zeitschrift für Chirurgie*, xxxvii., 1893.

undergoes a further mucous or hydropic change, forming a clear mucous or colloid-like substance filling up a cavity that may attain the size of a pigeon's egg. Through absorption of the contents of the cyst self-healing may take place. Chronic irritation is supposed to play the chief role in the production of this growth.

Tuberculosis.—The tuberculous affections of the bursæ may be primary or secondary. The growth of tubercles in the bursal membrane is usually associated with the production of a serous or serofibrinous exudate, producing a hygroma tuberculosum. Polypoid granulations may develop in the wall with formation of rice-bodies, or the cavity becomes filled with caseous material from caseation of the tubercles in the wall.

Syphilis.—Syphilitic affections of the bursæ are not so common as those of the tendon-sheaths, but are similar in nature and mode of occurrence.

Tumors.—The chondroma is the most common new growth of bursæ; other tumors are rare. Sarcomas and fibromas have been described.

THE DIGESTIVE SYSTEM.

WHEN we reflect upon the great extent of the alimentary tract, the variations in its anatomic structure, and the diverse nature of its functions, we are at no loss to understand why disturbances of this system bulk so largely in any study of general or special pathology.

Perhaps no system of the body is more abused than the alimentary, and yet it carries on its duties under conditions that might excite our wonder, even when we remember that the laws of adaptability and complementary function are especially exemplified in this system.

Any detailed description of the processes of digestion would be inadmissible here, but a rapid glance may not be out of place, as it will throw light on what is to follow.

The functions of the alimentary tract are, in brief, to ingest food-stuffs and by mechanical action to render them suitable for absorption and assimilation; to convert, by the secretory activity of the mucous membranes lining the digestive tube and of its accessory glands, substances which are largely insoluble, into those largely soluble, so that they eventually become converted into vital tissues and fluids; and, finally, to eliminate from the body those products which are unnecessary or actually harmful to the economy.

The digestive juices which bring about these changes are the saliva, gastric juice, bile, pancreatic juice, and the succus entericus.

The food-stuffs consist, when reduced to their simplest elements, of proteids, carbohydrates, fats, water, and certain mineral substances. These are acted upon variously in different portions of the digestive system, so that we may consider digestion as it occurs in the mouth, the stomach, or the intestines.

In the mouth the digestive agent is the saliva. It assists in mastication, by moistening and softening the food, and in deglutition. It dissolves certain mineral substances that are soluble in slightly alkaline fluids, and feebly emulsifies fat, but has little action upon proteids except that of maceration. Its most important function is, however, to change starches into some form of sugar.

When the food reaches the stomach, the alkaline product is neutralized by the action of the hydrochloric acid in the peptic secretion, and amylolytic action is stopped.

The activity of the stomach-juice depends upon pepsin. This has little or no action upon fats, except that it may dissolve the investing membranes and so liberate the fat. But the chief action is to convert proteids into albumoses and highly diffusible peptones. Whether absorption takes place to any extent in the stomach is doubtful, but at all events the main action of the stomach is, together with that just indicated, to churn and thoroughly mix its contents and then pass them on into the intestines for final treatment and ultimate absorption.

Passing on into the duodenum the food-stuffs are mingled with the bile, which by its alkalinity tends to diminish the activity of the pepsin. Bile has no digestive action on proteids, and its chief purpose is to act as a weak solvent of fats, to combine with fatty acids to form soaps, and to aid in absorption. Its antiseptic powers have been greatly overestimated.

The most powerful digestive agent of all is the pancreatic juice, which owes its qualities to three ferments. These convert starch into sugar, proteids into peptones, and, finally, emulsify fats, converting neutral fats into glycerin and their respective fatty acids.

That the pancreatic secretion is perfectly adequate to carry on the main functions of digestion without the assistance of the peptic ferment is seen in those cases in which the stomach has been removed, and it has been found that life could be prolonged apparently indefinitely. It is evident, however, that pancreatic digestion differs from peptic in some particulars, for in the former case, in the course of the digestion of proteids, two new bodies are formed—leucin and tyrosin—which prove that certain of the proteids are broken up into bodies which are no longer proteid in nature.

Among the supplementary products of pancreatic digestion should be mentioned indol, which is produced by the action of bacterial ferments upon the pancreatic secretion. If in the course of digestion by the pancreatic fluid bacteria are prevented from growing in the solution by antiseptic substances, no indol is produced. Indol in part may be absorbed, so that indican appears in the urine. The fact is of importance in certain pancreatic conditions.

The succus entericus is supposed to act in the same way as the pancreatic secretion, but much more feebly; it is also said to convert cane-sugar into lactic acid, and, finally, into butyric acid, with the evolution of carbon dioxide and hydrogen. Its digestive functions are probably of slight importance.

From a consideration of the complicated processes which make up the function of digestion, and the number of diverse structures and organs which are concerned in it, it will readily be grasped that lesions of the digestive system may arise from a great many different directions. It is a difficult task to assign to all the etiologic factors their proper places and proportions, for they can only partially be dissociated from one another. Disorder in the mechanism of the digestive tract hinders the due performance of its secreting functions, and vice versa; and alterations in the characters of the normal intestinal contents, brought about by mechanic or secretory defects, in their turn react upon the intestinal function, and eventually upon the general system. Thus a vicious circle is frequently brought about.

If the subject is complicated when the alimentary system is concerned merely with the digestion of ordinary healthy food, it becomes still more so when unsuitable or decomposed substances are ingested and the additional elements of mechanic, thermic, and chemical irritation are introduced.

Disorders of Secretion.—Inasmuch as the digestive action of the saliva is relatively slight, disorders of the buccal secretion and of that of the salivary glands are of but little importance except in so far as they lead to difficulty in mastication, deglutition, and speaking. In many infectious fevers, for instance typhoid and pneumonia, as Mosler has pointed out, the secretion of saliva is diminished, and this has also been noticed in diseases like cholera and diabetes, where there is excessive elimination of fluid from

the body. A real danger connected with the condition is that the mouth in such cases may become foul and lead to septic complications.

An increase in the amount of saliva secreted (ptyalism) is often met with, for example in all forms of stomatitis, in mercurialism, and in bulbar paralysis. Reflex ptyalism is met with in cases of gastric ulcer, pregnancy, trigeminal neuralgia, and hysteria. Occasionally the character of the secretion is altered; it may be defective in ptyalin or the reaction may become acid, as has been observed in diabetes, fevers, and certain dyspeptic conditions. This is due to the action of micro-organisms, whereby lactic acid is produced.

According to Arkovy, of Buda-Pesth, the bacteria found in the mouth in connection with diseased conditions are, in order of frequency, *B. gangrene pulpe*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Staphylococcus albus*, and *B. pyocyaneus*. The presence of pus-organisms is important, as they may lead to infective disorders of the stomach, catarrh, and atrophy of the glands, as Hunter has shown, thus paving the way for the absorption of toxic substances into the general system.

Another result of altered secretion is seen in the formation of concretions in the ducts of the various salivary glands.

The chief disorders of the gastric secretion are those connected with its quantity and the relative proportion of the hydrochloric acid. Diminution or complete absence of the peptic ferment is seen in advanced diseases, such as atrophy of the glands, carcinoma, and in some few nervous conditions, but is the last function to be interfered with.

Hypersecretion of the gastric juice is found in certain nervous affections—hysteria, neurasthenia, and tabes—and may or may not be associated with hyperacidity.

Diminished gastric secretion, chiefly of its hydrochloric acid constituent, is to be attributed to changes, either of an organic or functional nature, in the glands of the mucosa, and is found in atrophy of the mucosa, chronic catarrh, carcinoma, and amyloid disease, as well as in the various anemias and cachexias.

Hyperacidity is most frequently found in connection with gastric ulcer.

Hypoacidity (achlorhydria) often leads to defective action of the pepsin-ferment and delayed conversion of the proteid substances; but in some cases this does not seem to occur, the intestines being apparently able to do the work.

A very important result of the deficiency of the hydrochloric acid is that in this condition bacteria can flourish readily in the gastric contents. Normally bacteria can be found in the stomach, but are to a certain extent inhibited by the action of the acid. When proteid materials are combined with the acid the inhibitory effect is lessened. Thus, when an abundant meal of proteid substances is taken, bacteria may pass through the stomach comparatively little affected. An excess of bacteria in the stomach is found in cases of gastrectasis and impaired muscular action, and hampers the combination of the hydrochloric acid with the proteid materials. Certain of the bacteria by decomposition produce acetic, lactic, and butyric acids, carbon dioxid, hydrogen, and marsh-gas, thus causing acid dyspepsia, flatulency, and irritation of the gastric mucosa, besides impeding the action of the pepsin and hydrochloric acid upon the proteids.

But little is known about the anomalies of the intestinal secretion. By

far the most important point is the presence of various bacteria in the intestinal contents; here again stagnation of the food-stuffs within the bowel is a fertile cause of increased and abnormal bacterial activity.

The substances produced by bacterial activity are similar to those found in the stomach, with the addition of the products of the putrefaction of albuminous materials, sulphuretted hydrogen, and aromatic bodies. A great variety of affections have been attributed to these toxic substances.

Disorders of Absorption.—Pent-up products of abnormal fermentation lead to irritation of the intestinal mucosa, with increased secretion of mucus, hyperemia, and outpouring of fluid (diarrhea), while certain of the toxins are no doubt absorbed and give rise to systemic disturbances. Little is known about the details of these processes. Any influence that injures the lining cells of the mucosa or of the lymphatics and venous channels which carry off the products of digestion from the intestines leads to impaired absorption. This is seen in severe catarrhs, passive congestion, or tuberculous disease of the lymphatics. As a rule, the absorption of fat is chiefly interfered with; but in severe cases proteids and carbohydrates are also affected.

Disorders of Elimination.—These are in part mechanic or obstructive. Overfeeding, the development of gases, stenosis of the pylorus by ulcers or tumors, abnormal position of the stomach, atony of the muscle, all lead to dilatation of the stomach and retention of food-stuffs beyond the natural period, thus leading to an abnormal increase of bacterial activity with its associated results—irritation and disorders of absorption. Increased peristalsis in the intestine, together with the production of watery feces (diarrhea), is common. It may be due to irritation of the bowel by chemical or toxic substances, or may have a nervous origin (hysteria, neurasthenia, nervousness). Defective absorption of water from the intestinal contents may lead to the production of watery stools.

Constipation, the condition in which the stools are less watery than normal and are less frequently evacuated, may arise also from a variety of causes: too concentrated food, neglect, obstruction to the lumen of the intestine, overdistention, paresis or spasm of the muscular wall.

The intestine also assists in the elimination of poisons from the body, and this may give rise to alterations in the normal chemical processes that occur within its lumen and may lead to irritation. This is so in many infective fevers, in Bright's disease, and in certain other troubles due to disorders of internal secretion.

Gastro-intestinal Auto-intoxication and Auto-infection.—Gastro-intestinal auto-intoxication in the restricted sense is the condition in which toxic substances produced in the intestinal tract by abnormal chemical changes are absorbed into the general system and produce pathologic disturbances. Some authorities include under this head the intoxication arising from decaying proteid material—meat, sausage, milk, cheese, etc.; others again would exclude influences of an exogenous nature, such as bacteria, from the category. It is difficult, however, to separate those factors one from the other, so that it is more practical to consider them under the one classification.

The toxic substances may be derived from the normal digestive ferments and from the normal chemical substances produced in the function of digestion. Among these may be mentioned:

a. Those derived from proteids: Albumoses, peptone, tyrosin, indol,

skatol, phenol, fatty acids, leucin, acetone, ammonia, carbon dioxid, hydrogen, sulphuretted and carburetted hydrogen, cystin, and methylmercaptan.

b. Those derived from carbohydrates : Formic, acetic, propionic, butyric, valerianic, lactic, and succinic acids, acetone, and various gases.

c. From the fats : Fatty acids and glycerin.

Besides these may be mentioned those derived from bacterial activity : Fatty acids, diamins, pyridin and chinolin bodies, and toxalbumins. Bacteria themselves may be taken up and infection or subinfection produced. A great variety of disorders have been attributed to the absorption of these substances.

According to Albu,¹ the following types of affection due to gastro-intestinal auto-intoxication may be recognized :

1. Skin : *a.* Anemia, icterus, bronzing ; *b.* Erythema, urticaria, dermatitis.

2. Muscles : Polymyositis.

3. Alimentary tract : Vomiting, eructations, anorexia, diarrhea, constipation, and colic.

4. Urinary system : Albuminuria, hematuria, hemoglobinuria, acetonuria, oxaluria, cystinuria, increased toxicity of urine.

5. Central nervous system : Headache, dizziness, weakness, insomnia, dulness, coma, delirium, convulsions, paralysis, psychoses, disturbances of the circulation, respiration, and of the body-temperature.

6. Constitutional and diathetic diseases : Blood-disturbances, cachexia, diabetes, and uric-acid diathesis.

While the action of morbid ferments or bacterial toxins derived from the intestinal tract is being increasingly recognized as an important factor in the causation of systemic disease, there is another aspect of the subject, suggested by recent experimental work, which merits notice. This is the important fact that micro-organisms can be obtained by culture-methods from the normal organs of healthy animals, such micro-organisms for the most part being derived by vital absorption from the intestinal tract, as a number of different observations suffice to show.

Ruffer,² on examining sections taken from the small intestine of healthy rabbits, found that leukocytes were present upon the surface of the mucosa, others between the epithelial cells of the membrane, some of which contained microbes, while Peyer's patches contained immense numbers of micro-organisms apparently within the lymphoid cells. A similar condition was found in the case of the rabbit's tonsil.

Further, the leukocytes passing back from the mucous surface to the lymphoid follicles were taken up by certain large cells—macrophages—and were eventually digested together with any bacteria or food-stuffs they might contain.

Somewhat analogous observations have been made by A. B. Macallum³ in connection with the subject of the absorption of iron from the intestinal tract. He took a lake lizard which had been for thirty months without food, and fed it upon albuminate of iron. Killing such an animal after eight hours and removing and preparing the intestine, he found that within the lumen of the intestine were numerous free leukocytes crowded with granules

¹ *Die Auto-intoxikationen des Intestinaltrakts*, Berlin, 1895.

² *Brit. Med. Jour.*, vol. ii., p. 491, 1890.

³ *Jour. of Physiol.*, vol. xvi., p. 268, 1894.

of iron ; others, either free from iron or loaded with it, could be seen between the epithelial cells, while others were subepithelial. In the higher animals he found that the iron-containing leukocytes could be seen in the venules of the villi ; and, further, that many of the leukocytes in the capillaries of the liver and spleen were laden with iron.

Our own observations carry the investigation a step further. The first reference to the subject was in a paper upon the "Etiology of Chronic Bright's Disease,"¹ and the observation there made has since been repeatedly confirmed.

After killing healthy rabbits the mesentery of the small intestine was put on the stretch by means of a pair of sterilized forceps ; the surface was rubbed on both sides by a sterile cotton swab to remove the lining endothelium, and a portion of the transparent membrane was then cut out with sterile scissors and placed immediately into 10 per cent. formalin solution. The tissue was then stained in carbol-thionin, decolorized by acetic acid, and cleared in anilin oil and xylol ; all the steps being carried out in sterilized dishes. In carefully prepared specimens, almost invariably bacteria in various stages of disintegration could be seen within the capillary vessels, either lymphatic or venous, and others again in the meshes of the tissue, often grouped about the nuclei of certain cells, which were apparently wandering cells.

That this appearance is due to a vital process, and not to any eddies in the blood consequent upon the death agony, is proved by the fact that bacteria could be seen with the cells of the lining endothelium of the capillaries. A similar condition of things is also to be observed in the mesentery of cats, dogs, and in the human subject.

Bizzozero² and Ribbert³ further have pointed out that bacteria can be seen in the healthy mesenteric gland, and their observations have been amply confirmed.

Adami⁴ has made some important observations tending to elucidate the subject still further. He pointed out that in the livers and abdominal lymphatic glands of animals suffering from the so-called "Pictou cattle disease," in which there is a peculiarly extensive cirrhosis of the liver, there was present a minute diplococcoid micro-organism which it was difficult to stain satisfactorily. Somewhat similar bodies, though even more minute, were found in the livers of human beings dying from atrophic portal cirrhosis. These particles are recognized as well-formed shadows having a characteristic brownish color and a diplococcoid or diplobacillary form. Conversely, by inoculation of rabbits with *B. coli* of typical appearance, the inoculated bacteria were found in the liver in great numbers, all tending to assume the same diplococcoid or diplobacillary form. The germs were found within the liver-cells and in the endothelium of the capillaries. Cultures from the organs in cases of portal cirrhosis in some instances gave feeble growths of diplococci, which after repeated transfers developed into typical colon bacilli.

These granules formed in the liver were at first thought to be a possible cause of hepatic cirrhosis, but subsequent investigations showed that they were present in abundance in other conditions, and even in normal rabbits.

¹ *Canadian Journal of Medicine and Surgery*, December, 1899.

² *Centralbl. f. d. med. Wiss.*, xxiii., p. 491.

³ *Deut. med. Woch.*, p. 197, 1885.

⁴ *Montreal Medical Journal*, July, 1898.

These observations suggested a study, on analogous lines, of the kidney in Bright's disease and in normal animals, and we¹ were able to show that similar diplococcus-like micro-organisms were to be found in the kidneys in chronic Bright's disease and in some other conditions, most frequently seen in the secreting cells of the convoluted tubules, thus indicating that, like the parenchyma of the liver, the secreting cells of the kidney have some phagocytic properties. Subsequent observations proved that germs could be recognized in the kidney of the normal rabbit as well.

It has thus been demonstrated that bacteria can be recognized microscopically in normal tissues, but it remained to be proved that bacteria could be obtained by cultivation from such normal organs. In the paper "On the Etiology of Chronic Bright's Disease," already referred to, we were able in one instance to recover *B. coli* and the staphylococcus from the liver and kidney of a healthy rabbit when the organs were removed under strict antiseptic precautions, and subsequent investigations, notably by W. W. Ford,² have served amply to confirm the original observation.

Consequently we must conclude that micro-organisms are constantly passing into the animal economy from the intestinal tract even under normal conditions, and that they reach the liver and kidneys, where they are rendered practically inert. Whether the germs subsequently become active and lead to the production of actual disease depends upon other factors. As a rule, the tissues of the body are able to cope with the germs and render them innocuous, provided that they are not too virulent nor present in too great numbers.

To this condition Adami, in the annual address before the Chicago Society of Internal Medicine, Nov. 29, 1899, gave the name of "latent infection."

This latent infection probably explains those examples of terminal and "cryptogenic" infection with which we occasionally meet. We need only some cause which increases the virulence of the bacteria or depresses the vitality and resistance of the parenchymatous cells of the body to render such infection possible.

Apart from this, Adami recognizes a "subinfection," a "condition in which, as a consequence of chronic inflammatory disturbances in connection with the gastro-intestinal tract, there may for long periods pass in through the walls of the stomach or of the intestine a greater number of bacteria; and while the bacteria undergo the normal and inevitable destruction by the cells of the lymph-glands, the liver, the kidneys, and other organs, nevertheless the excessive action of the cells and the effect on them of the bacterial toxins liberated in the process of destruction may eventually lead to grave changes in the cells and in the organs of which they are part—changes of a chronic nature."

This theory of latent or subinfection, while it may not as yet have attained to the point of actual demonstration, certainly explains, as no other theory has yet done, those obscure cases, not only of concealed infection, but also of chronic proliferation of fibrous tissue which occurs so insidiously in the various organs. Perhaps to no disease would it apply with more force than to cirrhosis of the liver.

For years Hanot and his school have been urging the view that hyper-

¹ *Montreal Medical Journal*, March, 1899.

² *Trans. Assoc. Amer. Phys.*, vol. xv., p. 389, 1900.

trophic biliary cirrhosis (Hanot) was due to an infective agent. And when we consider the clinical manifestations, the enlarged spleen, the delirium, coma, the convulsive seizures, the eruption of petechial spots, the occasional elevation of temperature, and the leukocytosis, such an opinion seems certainly not unreasonable. The clinical resemblance of this form of cirrhosis to acute yellow atrophy, a disease almost generally admitted to be of an infective origin, is striking; in fact, the symptoms in both may be identical, the only difference being that in the former the liver is enlarged. Microscopically the resemblance is also close, for in acute yellow atrophy we see regeneration of the liver-parenchyma and a certain amount of interstitial change, together with the formation of new bile-ducts, just as in the case of cirrhosis, but with the addition of a severe necrosis of the liver-lobules.

With regard to atrophic cirrhosis (Laennec), Adami was perhaps one of the first to suggest that it was also of an infective nature, arguing from his investigations already referred to and from the suggestive fact that in cases of atrophic cirrhosis at postmortem there is so frequently found a succulent condition of the great omentum, enlargement of the mesenteric glands, perihepatic adhesions, and the occurrence of right-sided pleurisy, and the tendency of recent work upon the subject is to confirm this view.

Krawkow¹ observed that by giving microbic toxins by the mouth cirrhosis of the liver could be set up. He concluded that alcohol led to a gastro-intestinal catarrh, and then to the elaboration of toxins which, when carried to the liver, produced cirrhosis.

But it must not be forgotten that alcohol is not a prime factor in the causation of the condition, for, as Howard, Rolleston, and others have pointed out, atrophic cirrhosis has been found in young children and in those who never tasted alcohol; and conversely, the liver of chronic alcoholism is rather fatty than cirrhotic, as W. T. Kerr² has conclusively shown. Ramon³ fed different series of animals upon (1) alcohol, (2) bacterial toxins, (3) bacterial cultures, and (4) on alternating doses of alcohol and bacterial toxins. The animals fed upon cultures died of septicemia, and the effect upon the liver was to produce fatty degeneration, but no cirrhosis; the effect of alcohol was the same. In one case in which alternating doses of alcohol and toxins had been given, the animal after surviving ten months was found to show some hepatic cirrhosis. Ramon does not conclude that alcohol merely gives rise to a gastro-intestinal catarrh, but that its action was rather to promote absorption of toxins from the intestine and to diminish the power of the liver to resist them. For he found that in the case of a man taking alcohol the feces were actually less toxic than when no alcohol was taken; but, on the other hand, the urine contained more poisonous substances. Alcohol alone, then, does not deserve the blame.

Interesting in this condition is the view of Lancereaux,⁴ that in Paris cirrhosis of the liver is more common in those drinking wines than in those drinking alcohol in any other form. The poisonous substances he regards as sulphate of potassium, which is found in "plastered" wines in as great an amount as four to six grams per liter.

By feeding rabbits, guinea-pigs, and dogs from six to eighteen months with sulphate of potassium, he produced typical venous cirrhosis.

¹ *Arch. d. méd. exper. et d'anat. path.*, 1896.

² *Manchester Med. Chron.*, New Series, iv., pp. 225 and 310, 1895-6.

³ *Presse médicale*, April 21, 1897.

⁴ *Bull. de l'Acad. de Méd.*, Sept. 7, 1897.

Similarly Hanot,¹ in a posthumous contribution, is of the opinion of Budd, that cirrhosis of the liver may be due to the irritation produced by the absorption of certain products which are the result of disordered digestion.

Hanot and Boix were further able to prove that by administering butyric, lactic, and valerianic acids to rabbits atrophic cirrhosis could be produced. Histologically portal endophlebitis was found with a diffuse periportal productive hepatitis having a tendency toward the monocellular form.

Bindo de Vecchi² has reached some suggestive conclusions. He was able to produce suppurative hepatitis by the introduction of pathogenic germs into the liver. The lesions could be produced by injection of the germs into the bile-duct, the portal vein, or the intestine, but varied in intensity and distribution. He also produced proliferation of the interstitial connective tissue by the introduction of certain germs into the intestine. His experiments point to the pathogenicity of the colon bacillus. Before he could produce the lesions, however, it was necessary to weaken the resisting power of the liver, and this he did by obstructing the flow of bile.

This lack of resistance upon the part of the liver seems to be an essential factor in the process. The ordinary healthy liver seems to be quite able to cope with any germs which reach it.

Roger³ found by injecting various germs into the portal vein that the liver exerts a protective influence against some germs, while it has no effect upon or even assists the action of others. The anthrax bacillus and the *Staphylococcus aureus* are readily killed by it, while the growth of *B. coli* is promoted rather than otherwise. This protective action is lessened if the animal is kept without food. Small doses of glucose or ether by the mouth seem to increase it.

The experimental studies just cited all tend in the same direction, and show conclusively that inflammation of the liver can be brought about by the absorption from the intestine of toxic substances of the nature of the products of abnormal fermentation in the bowel, and that certain bacteria have a similar power, although in the latter case they tend to produce marked depression of the liver-parenchyma, acute suppurative disturbance, and even septicemia, rather than chronic proliferative change. Further, all point to the fact that before bacteria can act there must be a preliminary lowering of the vitality of the liver-cells. This can be brought about by the action of alcohol, certain organic fatty acids, and certain alterations in the physical condition. Here gastro-enteritis and intestinal auto-intoxication will play a part.

The theory of latent infection would focus all these various factors into one, for, granted that bacteria are normally present in healthy organs, they may remain quiescent until some outside influences are brought to bear whereby the vital resistance of the organ is lowered, or, what is practically the same thing, the virulence of the latent germs is increased. Whether we get then a chronic proliferative process, a suppurative one, or a general septicemia, will depend upon the correlation of all these various factors.

Schnitzler⁴ has published some interesting observations upon the latency of micro-organisms, which are of importance in this connection. On injecting frogs with virulent streptococci they remained in perfect health even up to forty-four days after injection; but if their vitality was lessened, as, for

¹ *Arch. gén. de Méd.*, Jan., 1899.

³ *Sem. médicale*, Oct. 19, 1898.

² *Lo Sperimentale*, An. liii., F. 3.

⁴ *Arch. f. klin. Chirurg.*, Bd. lix., Heft 4.

example, by exposure in an incubating-oven or by chloroformization, they sickened and died. Streptococci could be obtained by culture from the blood of such animals; while if other frogs similarly injected, which had not been subjected to the deteriorating process, were killed, the culture-tubes remained sterile. Thus he recognizes a latency of micro-organisms.

The general consensus of opinion seems to be that *B. coli* is the chief offending germ. This is ordinarily nonpathogenic; but we know from the researches of Macaigne¹ and Klecki that the virulence of this germ is greatly increased by disorders of the intestinal tract, such as gastro-enteritis, constipation, and strangulation, or other inflammatory affections. Further, the observation of Sanarelli² suggests that the action of certain other germs in the intestine may increase the activity of *B. coli*. Altogether, recent work certainly tends strongly to show that cirrhosis of the liver is really an infective process. We seem to be on the verge of great discoveries in this difficult field.

With regard to the avenues by which infection reaches the liver, in the case of atrophic cirrhosis it is largely by the portal vein; but in other cases it may be either through the general blood-stream or by the bile-ducts. Thus we can recognize three forms: portal, arterial, and biliary.

Weaver³ has shown that by the subcutaneous injection of a germ belonging to the colon group, obtained from guinea-pigs dying spontaneously, he could produce cirrhosis; and a similar observation has been made by Hektoen⁴ in the case of a bacillus of the pseudodiphtheric type; and from the fact that bacterial products introduced into the general circulation can produce cirrhosis, Rolleston has been led to think that the cirrhosis in some cases originates about the hepatic artery.

The fact that in scarlatina, as Klein has pointed out, an acute interstitial hepatitis so often exists, would seem to throw some light upon the occurrence of cirrhosis in children. A milder condition we have frequently observed in connection with typhoid fever and general tuberculosis. Kelsch and Kiener also pointed out the occurrence of a malarial cirrhosis.

That cirrhosis can be produced by obstruction to the outflow of bile, as, for example, by a calculus, is a matter of common observation. This is no doubt due in part to the lowering of the vitality of the liver-parenchyma in such cases referred to by de Vecchi; but in addition it must be remembered that calculus formation is but the result of a chronic or subacute catarrh of the bile-passages, probably originating in the intestine, so that the action of germs in this case must not be excluded.

Rolleston has described an instructive case of cystic liver due to congenital obstruction of the bile-ducts, in which the growth of connective tissue about the bile-ducts was well marked. Biliary cirrhosis has also been produced experimentally by ligature of the common bile-duct.

Apparently we have no fibroid changes in the liver due to arteriosclerosis analogous to those in the kidneys and some other organs; and it is more than probable when arteriosclerosis is present that it is really secondary to the fibrous-tissue proliferation about the vessels.

With regard to the entrance of germs through the general circulation into the liver, we must be careful not to limit such an invasion to the agency of the hepatic artery alone; for if toxins or bacteria are circulating in the

¹ *Arch. gén. de Méd.*, Dec., 1896.

² *Ann. de l'Inst. Pasteur*, pp. 193 and 353, 1894.

³ *Trans. Chicago Path. Soc.*, vol. iii., p. 228, 1900. ⁴ *Jour. Path. and Bact.*, vii., p. 214, 1901.

blood, they must reach sooner or later the portal blood, when they will be returned to the liver, and in the process of excretion will reach the bile-ducts, where they may set up inflammatory processes. Thus we see that it is too partial a view to regard cirrhosis as divided into portal, arterial, and biliary varieties by any arbitrary lines. In fact, in whatever way a cirrhosis may start, it sooner or later becomes mixed in type, and this not only in regard to the avenues by which infection reaches the organ, but also to histologic appearances and clinical manifestations.

Thus fibrous-tissue overgrowth about the portal vein must in time implicate more or less the bile-passages and the hepatic artery.

Besides the portal, biliary, and hepatic forms of cirrhosis just referred to, we have certain others, viz., the pericellular, the Glissonian, and the centrilobular.

In the first, which is seen typically in both congenital and acquired syphilis, in Pictou cattle disease, and in Hanot's cirrhosis, there is a peculiarly diffuse development of connective tissue of a transparent appearance with little tendency to contract, and at the same time, except in certain cases of syphilis, there is remarkably little cellular infiltration. In contradistinction to atrophic portal cirrhosis, the connective tissue surrounds only lobules or small islets of liver-cells, so that there is a generalized atrophy of liver-parenchyma, and the resulting fibrosis is probably of the "replacement" type. This form is also probably of infective origin, but more cannot as yet be said.

Glissonitis (*Zuckergussleber*) is characterized by great thickening of Glisson's capsule, in which strands of connective tissue in some cases pass into the hilus and produce cirrhosis exactly analogous to the induration of the lung which sometimes follows chronic pleurisy and peripneumonia.

The form of cirrhosis resulting from passive congestion is of little importance; fibrosis about the intralobular vein does occur in advanced cyanotic congestion of the liver, but the changes are rather those of pressure-atrophy than of cirrhosis.

An interesting condition associated with cirrhotic changes in the liver and pancreas has attracted considerable attention lately; this is the so-called hemochromatosis of von Recklinghausen.

As early as 1871 Troisier had noted the occurrence of bronzing of the skin in diabetes; but the work of Hanot especially, who observed that bronzing also occurred in connection with cirrhosis of the liver, seems to have stimulated the important researches of Letulle, Marie, and others of the French school. While the French observers largely took up the subject in connection with diabetes, the Germans (Quinke, von Recklinghausen, Hintze, and Kretz) attacked the larger question of pigmentation in relation to blood destruction.

Quinke, in 1877, pointed out the occurrence of an iron pigment, hemosiderin, in the liver in cases of pernicious anemia; von Recklinghausen, in 1889, described a generalized pigmentation involving the skin, the liver, the spleen, the pancreas, and most of the glands of the body. In some of his cases there was cirrhosis of the liver, which he regarded as due to a hemorrhagic hepatitis. These observers isolated two pigments—hemosiderin, which contained iron, and hemofuscin, which did not.

The subject has until recently received little attention from English or American observers. Saundby, in Allbutt's *System of Medicine*, vol. iii.,

has a brief reference to it. Osler¹ reports 2 cases of hypertrophic cirrhosis with hemochromatosis, but without diabetes.

A valuable contribution to the literature is that of Opie, Jr.,² in which he gives an able discussion of the subject. He regards hemochromatosis as a distinct morbid entity "characterized by the widespread deposition of an iron-containing pigment in certain cells and an associated formation of iron-free pigments in a variety of localities in which pigment is found in moderate amount under physiologic conditions." He further thinks that the pigment accumulation leads to degeneration and death of the containing cells, and subsequent fibrous proliferation in the liver and pancreas, amounting to cirrhosis of these organs with hypertrophy, and he thinks when the chronic interstitial pancreatitis has reached a certain grade of intensity diabetes is the result.

We apparently have to recognize two conditions—cirrhosis of the liver with hemochromatosis, the cirrhose pigmentaire of the French school, and the much commoner combination of cirrhosis of the liver and pancreas—hemochromatosis and diabetes—the so-called diabète bronzé.

Anschutz³ records a case of hypertrophic cirrhosis of the liver, cirrhosis of the pancreas and resulting diabetes, and has collected 24 cases of such a condition. Of the 24, the liver showed the changes of pigmentary cirrhosis in 23; all the cases were in men. Twenty-one of 22 cases showed involvement of the pancreas; and in 18 cases in which microscopic examination was made, pigment was discovered in various organs. Only a few cases occurred without diabetes.

Maude Abbott⁴ records a case of pigmentary cirrhosis in a woman aged fifty. The liver was rather of the atrophic type. There was no diabetes. Microscopically, cirrhosis of the liver and pancreas was found, but none of the kidneys, with more or less hemosiderosis.

The absence of diabetes Abbott is inclined to explain on the assumption that the pancreatitis was not sufficiently advanced to hamper materially the function of the organ, or else that the diabetes was latent while the patient was under observation, which, as Marie has pointed out, can occur. With regard to the frequency of hemosiderosis, Kretz found it in 14 of 26 cases of cirrhosis of the liver; and Abbott in 6 of 16. Abbott also found hemosiderosis in liver and spleen in 4 cases of 41, apart from the conditions of cirrhosis or pernicious anemia. In these cases there were evidence of localized blood destruction and a history of some intestinal disturbance. It is suggestive, as Hintze points out, that the earliest stage of recognizable hemosiderosis is found in the walls of the small intestine. In general, Abbott's conclusions are that there is somewhere in the body an increased destruction of hemoglobin, a degeneration of the cells of certain organs by which they are unable to throw off the pigment deposited in them, and finally disintegrate, and that the cirrhosis is of the nature of a chronic interstitial inflammation secondary to the presence of the pigment. She finally suggests that the agency leading alike to blood destruction and to cell degeneration may be bacterial in its nature. She dissents, however, from Opie in that she does not feel assured that hemochromatosis is a distinct morbid entity.

Another disease which it seems probable that we shall have to regard as

¹ *Brit. Med. Jour.*, Dec. 9, 1899.

² *Jour. of Exper. Med.*, iv., 1899.

³ *Deut. Arch. f. klin. Med.*, lxi., 1899.

⁴ *Journal of Path.*, vi., p. 315, 1900.

of the nature of an infection from the gastro-intestinal tract is pernicious anemia.

Hunter¹ has given us a most valuable contribution upon the etiology of this disease. His first investigations, extending from 1885 to 1888, pointed to the conclusion that pernicious anemia was due to the hemolytic action of some special poison elaborated and absorbed from some part of the gastro-intestinal tract. Further investigation showed that these toxins were not simply an exaggeration of ordinary fermentative and putrefactive processes, but really of an infective origin. Certain local conditions, such as malignant disease, gastritis, atrophy of the gastric glands, predisposed to this infection. In his latest communication he is still convinced of the infective nature of the disease, and points out that the point of absorption is mainly the stomach, but in addition the buccal and intestinal mucosæ. The influence of carious teeth, stomatitis, and glossitis in inducing infective gastritis is dwelt upon. Treatment of some of his cases by antiseptics, such as salicylic acid, was followed by prompt improvement. The nature of the infecting agent is not clear, but certainly is not the ordinary germs found in the mouth or in the case of dental decay, but something with greater hemolytic powers. Hunter suggests that it is of a mixed nature.

The observations of Anderson and Ford suggest that latent infection here plays a role; but how far the *B. coli* or the various streptococci and cocci found by Hunter contribute to the condition needs further elucidation.

THE MOUTH AND ACCESSORY STRUCTURES.

Congenital Malformations.—Abnormities in the development of the oral cavity are frequently found, and certain of them are of considerable practical importance, since they may interfere with the functions of speech or the proper ingestion of food, and consequently may demand surgical interference.

Perhaps the most important is *cleft-lip* and *cleft-palate*. The fissure is always situated to one side of the median line, or, when bilateral, on both sides, at the points of junction between the intermaxillary bone and the supramaxillaries. All grades of the condition exist, from a slight depression on the edge of the lip to a deep cleft which extends into the nasal cavity. Very often the fissure extends into the hard palate and even into the soft palate; in the latter case the fissure takes the median line. An abnormally large mouth (macrostomia) or an unusually small one (microstomia) is occasionally met with. Complete absence of the mouth (astomia) is very rare. The tongue may be doubled or cleft at the tip (snake-tongue).

Abnormal shortness of the frenum of the tongue not infrequently occurs, and newborn children should always be examined for this condition, as it interferes with nursing, and should be remedied at once.

Defects in the development of the jaws (agnathia, brachygnathia, ateloprosopia, etc.) are occasionally met with.

Defects in the teeth are numerous, but the only ones of any importance are the defects of form. According to Hutchinson and others, certain peculiarities are associated with congenital syphilis. The upper central incisors are the ones affected. They are peg-shaped, short, and thin, the top being

¹ *Lancet*, Jan. 27, Feb. 3 and 10, 1900.

smaller than the crown, and there is a small concave notch upon the cutting-edge. The color is often more yellow than that of the unaffected teeth. The condition is not absolutely pathognomonic of congenital syphilis, as it is found in other conditions, notably rickets.

Circulatory Disturbances.—The circulatory disturbances found in the buccal cavity are of more clinical than pathologic importance. **Anemia** of the mucosa is readily recognized, and is a sign of general anemia. Local anemia of the soft palate is frequently associated with laryngeal and pulmonary tuberculosis, as has been pointed out by several observers.

Active hyperemia is a sign of local irritation, or may occur in connection with the various infectious fevers.

Passive hyperemia, in which the lips assume a reddish-purple color, is found in the various forms of obstructive cardiac and pulmonary diseases, and is an important clinical sign.

Inflammations.—Catarrhal Stomatitis.—The mucous membrane of the lips, tongue, cheeks, and alveolar process is reddened, swollen, and covered with excretion in which can be found desquamated epithelium. The papillæ of the tongue often swell, giving it a warty, granular appearance. At first the excretion contains relatively few cells, but later extravasated leukocytes and desquamated epithelial cells. If this exudate be allowed to remain, it is transformed into a dirty grayish-white or brown coating, which is specially thick about the tongue and the roots of the teeth. The coating often dries, and the tongue and lips become fissured or ulcerated. This event is a not infrequent cause of the secondary septic complications in the course of the infective fevers.

Catarrhal stomatitis and glossitis are frequently brought about by mechanical and chemical irritants, and are an almost invariable accompaniment of the infective fevers.

Aphthous stomatitis is accompanied by all the features of a catarrhal affection, but in addition it is characterized by the appearance of small grayish or yellowish-white spots, either singly or in groups, and situated most frequently upon the lips and tongue. These specks have a dull, opaque appearance and are surrounded by a bright-red hyperemic zone. The areas frequently coalesce, so that large patches are formed. According to E. Fränkel, the essential nature of the process is a fibrinous inflammation. The condition is usually found in children who are badly nourished or suffering from some irritation of the buccal mucosa. It is found also, however, in women at the menstrual periods and during pregnancy and the puerperium. It has also been observed in those who have been on protracted sprees.

Ulcerative Stomatitis.—This is an acute affection, rarely chronic, which begins about the gums at the bases of the teeth; at first the tissues are red, swollen, and the gums loosen somewhat from about the teeth. Owing to the edema the gums form warty projections. Later the affected tissues become paler, friable, and ulceration takes place, penetrating quickly the deeper structures. The necrotic process can extend to the lips and cheeks and to the periosteum of the jaw, leading to sequestration of the bone.

The affection occurs in those who are badly nourished or have become weakened by long-standing disease. Certain poisons, as mercury, phosphorus, lead, and copper, can also cause it. The affection is usually accompanied by marked salivation, and the mouth exhales a peculiarly penetrating, offensive odor.

Gangrenous stomatitis or noma can supervene upon the last-mentioned affection or can begin independently. In the first event the tissues are rapidly converted into a soft, pulpy, and fetid necrotic mass. In the latter the affection begins as a livid, swollen patch on the mucous membrane of the cheek, near the corner of the mouth.



FIG. 243.—Noma of the face (case of A. T. Bazin).

Small blisters may form and a local grayish-yellow inflammatory infiltration occurs, which is rapidly transformed into a gangrenous area. The condition rapidly spreads to the skin of the cheek, which soon assumes a reddish-black color. Just outside of the affected area the tissues are markedly infiltrated and edematous.

The condition is generally unilateral, but may affect both sides, and may spread to such an extent that the nose and jaw-bones are involved. Only rarely does the condition heal. Septic complications generally ensue and death is usually rapid. The affection is most common between the ages of two and twelve. Those in unhygienic

surroundings, badly fed, or debilitated from disease, are the most frequent victims.

From clinical and pathologic considerations it would seem clear that the disease is infectious in origin, but no specific germ has as yet been clearly proved to be the cause. A bacillus resembling that of diphtheria has been described by Bishop and Ryan, and Schimmelbusch, but is not invariably present. Babes and Zambilovici have isolated a pathogenic organism capable of inducing gangrene when inoculated into rabbits. Ranki and Lingard have also described a germ which they regard as specific. These investigations, however, need to be confirmed, and further research is necessary.

Suppurative Stomatitis and Glossitis.—This may occur by the extension of suppurative processes, erysipelas, and the like, from without, but is more frequently found in the tongue and gums as a result of traumatism, infected fissures, or as a complication in certain of the infections and in Bright's disease.

We have recorded one case of suppurative hemiglossitis in typhoid fever,¹ and Thomas McCrae² has recorded another and has collected five more from the literature. It appears to be an uncommon complication in typhoid fever. The condition may be diffuse and phlegmon-like, or multiple local abscesses may be seen. The whole tongue or any portion of it may be affected.

Tuberculosis.—Tuberculosis usually arises from tuberculosis of the face, lungs, or larynx, but is occasionally primary. Primary tuberculosis and that arising in the course of the pulmonary or laryngeal affection are most frequently found in the tongue, palate, and on the tonsils. Superficial nodules of a granular appearance are produced or the process may extend deeply into the tissues; all the typical appearances of a tuberculous focus are seen, and from caseation irregular ulcers with infiltrated edges are produced.

¹ *Montreal Med. Jour.*, p. 104, 1896.

² *Bull. Johns Hopkins Hosp.*, ix., 118, 1898.

Syphilis.—Occasionally the primary sore or chancre appears upon the lip or the tonsil, but secondary and tertiary manifestations are more common. The simplest form of the affection in the secondary stage is a simple erythema or angina, but the typical appearance is that of small flat papules surrounded by an inflammatory zone. Later the superficial epithelium becomes of a pearly, bluish-white color resembling the corrosion produced by silver nitrate (*plaques opalines*). These occur usually upon the lips, cheeks, and tongue, but also upon the gums, tonsils, and pharyngeal wall. They may go on to superficial ulceration and small fissures be produced. Healed radiating scars about the angles of the mouth in young children are characteristic of syphilis. Gummas are found most frequently in the posterior wall of the pharynx, the palate, the gums, and the tongue.

Thrush.—Thrush is an infectious process brought about by a fungus, the *Oidium albicans*, whereby on the tongue, and the inner sides of the cheeks especially, small white patches are produced, which may coalesce and give rise to a membrane-like deposit. This at first is white, but from uncleanness may become yellowish brown or black.

When removed the epithelial surface is reddened or may show minute superficial ulcers. The growth of the fungus begins in the epithelial layer, but may invade the deeper structures. Children in the first year of life are most subject to the disease. The use of milk and starchy foods, together with imperfect cleansing of the mouth, assists the development of the condition. It is found only in adults that are run down, and sometimes develops in the course of infectious diseases.

Actinomycosis.—The infection of man by ray-fungi is on the whole rare, but is perhaps more frequent than has been supposed. The most usual entrance-point is the mucous membrane of the mouth and pharynx. In many instances the site of infection seems to be at a carious tooth. Israel and Partsch have demonstrated the fungi in the cavities of decayed teeth. Cases are reported in which infection has followed picking the teeth with a stalk of hay or, as in the case of tailors, putting a needle into the mouth. A few instances are on record in which gumma-like tumors due to actinomycosis have been present upon the tongue. One of these is described by Claisse.¹ When the jaw is attacked the growth at first resembles periosteal sarcoma, but, according to Senn, when the looser tissues of the neck are reached the growth is very rapid, particularly along the line of the fascia. Before suppuration sets in, if an incision into the tumor be made, minute yellow points can be seen, which are the actinomyces. When a purulent discharge is present search should be made for the fungi, which are present as yellowish dots about the size of pin-heads or smaller. These can be picked out and examined with a low-power lens or a film may be made and stained by Gram's method. In human actinomycosis the filaments are apt to lack the usual clubbed appearance.

From the soft tissues of the face and neck the process may extend to the brain and spinal cord and their coverings, and also to the organs of the chest.

Tumors.—The most important tumors found in children are the **hemangioma** and the **lymphangioma**. The former is usually found upon the lips, and forms dark bluish-red, slightly elevated blotches. Under the

¹ *Jour. of Laryng.*, May, 1897.

latter form are included macroglossia and macrocheilia. The tongue and lips are greatly enlarged owing to an increase in all the tissue-elements, from increase of the fibrous tissue alone, or, finally, from tumor-like masses—true lymphangioma. In this condition the tongue may become so large that it projects beyond the teeth and may reach double its normal size. By pressure it leads to deformity of the bony structures, and owing to its size may interfere with feeding and respiration. The surface often becomes dry and fissured, or ulcerated from pressure upon the teeth. Microscopically the tissue is seen to be riddled with small cavities representing the dilated lymphatic vessels lined by endothelium; the dilatation may become so extreme that actual cysts are produced.

Among other tumors, either congenital or developing soon after birth, may be mentioned teratoma, lipoma, fibroma, myxoma, and sarcoma. Teratomas frequently develop from the palate or vault of the pharynx; they are either due to inclusions of cells within the fetus or are to be regarded

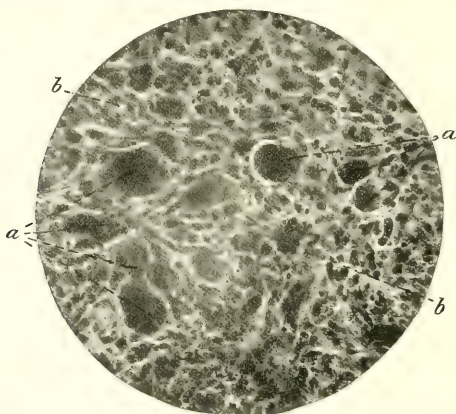


FIG. 244.—Giant-cell sarcoma of the alveolar process: a, large multinucleated cells; b, mixed sarcoma-cells.

as unequal and undivided twin formations. In adult life sarcomas and carcinomas are more common.

Giant-cell or myeloid **sarcomas** are found oftenest upon the gums and develop from the periosteum or bone-marrow of the jaw. They form round nodular tumors of fairly firm consistence. From hemorrhage they frequently have a brick-red color. Other forms of sarcoma are not infrequently found.

Carcinoma is found upon the lip, tongue, or the gums. It begins as a small elevated papule, or as a firm, circumscribed, whitish-gray infiltration of the mucosa. The surface ulcerates, and the ulcer more or less quickly invades the neighboring parts.

Cysts due to obstruction of the various ducts discharging into the oral cavity are not infrequently found.

THE TEETH.

The most important affection is **caries**. This begins as an opaque white, or more often a greenish or greenish-black, speck upon the enamel, due to disintegration and destruction of the enamel-prisms. As the process advances the center of the tooth becomes hollowed out and the whole tooth eventually undergoes decalcification and softening. Very frequently caries is accompanied by inflammation of the pulp—pulpitis—or of the periosteum of the alveolar process.

Inflammation of the pulp or about the root of the tooth may result in suppuration, so that the gum in the neighborhood is reddened and swollen. Local abscesses can thus be produced, which may lead to external fistulæ or sequestration of portions of the jaw. In chronic nonsuppurative inflammation of the pulp and periosteum, granulation-tissue or even new bone or dentin may be developed. The condition is due to infection with various germs. According to Miller, acid fermentation of food-particles clinging about the teeth assist the action of the bacteria. Pepsin and various vegetable acids, according to Schlenker, are responsible for the destruction of the dentin.

Of tumors, the odontoma, odontinoids, sarcoma, fibroma, and myxoma are recorded. The odontoma is developed from the pulp during the growth of the tooth or forms excrescences about the crown or root. Those forms developing in later life from the dentin or cement substances are called odontinoids. Sarcoma and other connective-tissue tumors develop but rarely from the pulp during the periods of development, but most frequently are derived from the periosteum about the tooth or jaw. Falkson has drawn attention to a cystadenoma or multilocular cyst, lined with cylindric epithelium, developing from embryonal tooth-follicles, and containing teeth.

PALATE, PHARYNX, AND TONSILS.

The mucous membrane of the palate, pharynx, and tonsils bears in general a great resemblance to that of the other portions of the buccal cavity, but differs in this respect, that its character as a mucous membrane is even more pronounced, and still more in that it is rich in lymphoid elements both in the form of follicles and in the larger aggregations of lymphatic structures that form the tonsils. Consequently desquamative processes here are less important, while exudative ones become more important.

It has been found that the tonsils perform an important function. Leukocytes can be found in the glands, and often form well-marked masses that may pass through the epithelial covering, forming a thick layer upon the surface. The leukocytes are phagocytic, and thus suggest that the tonsils act as sentinels at the portals of the pharynx to deal with invading germs.

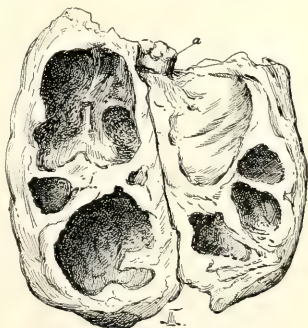


FIG. 245.—Multilocular dentigerous cystoma of the mandible: a, tooth.

Thus it is that the tonsils may become an important point of entrance for infection into the system.

Inflammation of the pharynx, palate, and tonsils, designated as **angina** or **pharyngitis**, is of frequent occurrence. It is often the result of irritation from mechanic, thermic, or chemical causes, and is frequently seen in connection with many infectious diseases, notably scarlatina, measles, diphtheria, variola, and acute rheumatism. When the tonsils are chiefly or alone affected, the condition is spoken of as **tonsillitis**.

In the catarrhal form the mucosa is reddened and swollen, and the surface is covered with a mucoid or mucopurulent secretion, sometimes mixed with blood, or it may have a more whitish color from admixture with desquamated epithelial cells. Occasionally vesicles resembling herpes may be seen.

In **catarrhal** or **follicular tonsillitis** the surface is covered with a similar secretion, which collects in the lacunæ of the glands and produces whitish-yellow plugs. When the condition subsides the plugs may remain, become inspissated, and infiltrated with lime salts, so that concretions are formed. These pellets have a characteristic unpleasant smell. The amount of swelling of the tonsils depends on how far the inflammation is a superficial or a parenchymatous one.

Chronic pharyngitis may develop insidiously or succeed upon a series of acute attacks. The appearances vary at different stages. At first the mucosa is more or less reddened and covered with distended venules; often it has a granular or warty appearance, supposed to be due to hyperplasia of the lymphoid follicles (granular pharyngitis). The secretion is mucoid, mucopurulent, or purulent, and often adheres in the form of dry crusts or scales having an offensive odor. In other cases the secretion is slight and the mucous membrane reddish brown, thin, smooth, and shiny. This condition is due to atrophy of the mucosa.

Hyperplasia of the tonsils, including Luschka's, is often found in children, and is probably in many instances due to a chronic inflammatory process that leads to a proliferation of the lymphoid structures. The enlargement may be so great as to interfere with swallowing, and is important since it tends to perpetuate any inflammatory trouble present. Children with a rheumatic taint seem to be specially liable.

Adenoid vegetations are due to a hyperplasia of the pharyngeal tonsil and to an actual new formation of lymphoid tissue, whereby soft papillomatous masses fill up the vault of the pharynx and the posterior nares to such an extent that breathing is interfered with. Owing to interference with the Eustachian tubes either by pressure or catarrh, deafness and inflammation of the middle ear may result. Children so affected breathe through the mouth, complain of headache and earache, and are often apathetic and backward at school. In long-standing cases the chest has a characteristic deformity.

In **phlegmonous inflammation** the process is less marked upon the epithelial surface than in the deeper tissues. Cases are primarily due to infective micro-organisms, in some cases assisted by trauma, or occurring as secondary complications of certain infectious fevers, such as erysipelas, diphtheria, syphilis.

Retropharyngeal abscesses may result from disease of the cervical vertebrae. The mucosa is of a deep purple-red color, moderately swollen,

tense, and shiny, with occasionally superficial vesicles. In the erysipelatous form the affection is diffuse and the exudate of a serocellular nature rather than a purulent one.

In other cases suppuration is common, so that quite large abscesses may form. Peritonsillar abscess or quinsy may occur upon one side or upon both. The abscesses may break into the pharynx, or if deep down the pus may be absorbed and a scar formed. One danger, apart from the risk of suffocation, is that the abscess may erode the internal carotid artery or some of its branches and cause fatal hemorrhage; gangrene is a terminal event, though a rare one; general septicemia also occurs.

Membranous pharyngitis (croupous or diphtheritic) may occur in the course of the various infections, like scarlatina, measles, typhoid, and variola, but is found in its most dangerous and typical manifestation in diphtheria.

This form is characterized by an inflammation due to the Klebs-Löffler bacillus, situated usually upon the palate, tonsils, or pharynx, but which may also spread to the nose, larynx, and bronchi. The cervical glands are generally enlarged.

The condition begins with marked hyperemia and swelling of the mucosa, but very quickly assumes the form of a membranous inflammation. At first there appear small grayish or grayish-white opalescent patches upon the tonsils, uvula, or other portions of the pharyngeal wall. The patches of membrane later become of a dirty yellow or yellowish brown, and may be slightly separated from the subjacent tissues at the edges and surrounded by a hyperemic zone. If the membrane be removed, there is seen to be a superficial necrosis of the mucosa, which bleeds readily. The membrane may again form upon the denuded area with great rapidity; sometimes the membrane is found to consist of several distinct layers.

In severe cases extensive necrosis takes place, so that there appear to be large gangrenous excavations about the pillars of the fauces. In other cases the membranous patches become confluent, and may form thick masses extending into the nasal cavities, trachea, and larynx.

By examining a series of sections at different periods it is found that the mucous membrane is at first hyperemic and more or less infiltrated with inflammatory material; the surface-epithelium is degenerated and desquamates either wholly or in part, and what remains is infiltrated with a cellular exudate which coagulates, forming a fibrinous deposit both in the superficial layers and upon the surface. This material, composed of degenerating tissue, leukocytes, and fibrin, next undergoes a form of coagulation necrosis and fuses into a more or less homogeneous mass—the diphtheritic membrane.

In the deeper tissues the blood-vessels and lymphatics are distended, there are numerous areas of cellular and croupous exudation, and the glands are blocked with exudate and desquamated cells.

Absorption of the exudate and regeneration of the surface-epithelium take place without scarring.

Tuberculosis.—This can affect the tonsils and pharyngeal wall primarily, but is more often found in those suffering from pulmonary or laryngeal tuberculosis.

Typhoid.—An ulceration of the posterior pharyngeal wall is occasionally met with in typhoid fever.

Syphilis.—The primary chancre has been found upon the tonsils and palate, but the usual lesions are the mucous plaques of the secondary stage and the gummatous form.

Cervical and prevertebral **actinomycosis** may start in the tonsils and the pharyngeal mucous membrane.

Connective-tissue **tumors**, carcinoma, and teratoma occur in this region. Sarcoma of the tonsil is occasionally met with.

THE SALIVARY GLANDS.

These have the structure of acinous glands in the human subject, having a serous or mixed serous and mucous type, and discharge their secretion into the oral cavity. The chief affections are inflammation and tumor formation.

Epidemic parotitis (*mumps*) is an infectious disease, of which the micro-organism has not yet been isolated, characterized by great swelling of the parotid gland and, generally to a less degree, of the submaxillary and sublingual glands, and associated with slight febrile disturbance. The infectious agent presumably enters through the excretory duct; in the ordinary form resolution takes place in the course of a few days. The affection is sometimes complicated by orchitis or oöphoritis.

Analogous involvement of the glands is found in the course of certain infectious fevers, as typhoid, cholera, pyemia, diphtheria, and syphilis. Some of these forms are apt to result in suppuration and even gangrene. When death does not take place in such cases fibrous induration or salivary fistulæ may result. Parotitis has also been observed as a complication of certain abdominal diseases and after operations upon the abdominal viscera.

Milder catarrhal inflammation of the ducts and acini may lead to increased secretion and the formation of concretions of phosphate or carbonate of lime. In such cases the ducts and acini are dilated and the gland shows fibrous induration, with possibly suppurative inflammation in parts.

Angina Ludovici is a rare, rapid, and fatal form of phlegmonous inflammation of the tissues about the floor of the mouth and sides of the neck. It apparently starts from trauma or some lesion about the roots of the teeth or the submaxillary gland. The floor of the mouth and the neck present diffuse dull reddening, and exhibit a brawny induration. It may end in suppuration or gangrene and frequently leads to general septicemia.

Of the **tumors** found in the parotid may be mentioned myxoma, fibroma, enchondroma, rhabdomyoma, sarcoma, and endothelioma. Perhaps the most important and characteristic are endothelioma and enchondroma; the latter is usually not a pure growth, but is mixed with fibrous and myxomatous elements. It has a distinct tendency to sarcomatous change. Carcinoma is rare.

THE ESOPHAGUS.

Affections of the esophagus are, on the whole, relatively uncommon. Some, however, are of great clinical importance from the fact that disease of this tube may interfere with the due passage of food into the stomach, and thus hamper nutrition.

As would be supposed, most of the affections are due to the effects of the passage of food or other substances that bring about either mechanical, chemical, or thermic lesions; or, again, to the extension of disease from

neighboring parts. The esophagus, from its situation, is particularly liable, for instance, to the effects of pressure.

Unlike that of the pharynx, the esophageal mucosa is poor in blood-vessels, lymph-elements, and mucous glands, and its epithelium forms a thick layer overlying somewhat prominent papillæ, so that this gives it an appearance not unlike that of the skin, and considerably modifies morbid processes. The tissue is also liable to postmortem change, so that care must be taken not to confound such with the effects of disease. Thus, the esophagus frequently shows a maceration and swelling of the epithelium, which presents the appearance of shreddy patches of a grayish, sodden character, situated on the longitudinal furrows. In more advanced grades the deeper layers show a gelatinous softening, often of a dirty reddish-brown color and friable. In still other cases there is actual perforation analogous to the postmortem digestion of the stomach.

Malformations.—These may exist alone or in common with other defects. The most common is for the upper third of the esophagus to end in a blind tube, often dilated, while the lower portion forms a fistulous communication with the trachea or a bronchus. There may be complete defect of any intervening portion, or more commonly the two ends are united by a fibrous cord. Local areas of stenosis are recorded, and in rare cases the lumen is partially occluded by a ring-like fold of mucous membrane.

Circulatory Disturbances.—Owing to the relatively few blood-vessels in the esophagus, hyperemia is rarely a striking condition. **Active hyperemia** is found in inflammation, in various infectious diseases, in newborn children, and in drunkards. It is also due to the irritation of certain articles of food. Hemorrhage may be due to passive congestion or ulceration. **Passive congestion** is found under the same conditions as it occurs elsewhere in the body. It is of importance, for it sometimes leads to the formation of varices. Thus, in cirrhosis of the liver the veins of the lower part of the esophagus are dilated, tortuous, and may give way or ulcerate, leading to fatal hemorrhage.¹

Retrogressive Changes.—**Atrophy** and **degeneration** have been described, but have been little studied. Of more importance are the various forms of **necrosis**. A common variety is due to the action of foreign bodies lodged in the lumen of the esophagus or to the pressure of tumors or aneurysms from without. These produce at first a pressure-atrophy and ischemia, which rapidly lead to ulceration.

Gangrene has been observed in a few cases, as an extension of noma of the cheek or pharynx, gangrenous tonsillitis, or gangrene of the lung. In rare instances peptic ulcers develop.

Inflammations.—The commonest form is **catarrhal esophagitis**, which is due to the action of thermic or chemical irritants in the ingesta or occurs as a complication of many of the infectious fevers. It is characterized by a heaping up and desquamation of the superficial epithelium, together with an increase in secretion which may lead to the formation of scattered shallow ulcers. These are usually situated on the top of the longitudinal folds, and may heal with the formation of small scars.

If the cause persist for any length of time or be frequently brought into play, a chronic catarrh results, with the production of a more livid color,

¹ For a comprehensive study of esophageal hemorrhage in cirrhosis of the liver, see Preble, *American Journal of Medical Sciences*, cxix., 263, 1900.

epithelial thickening, and productive change. The epithelium may form papillomatous or polypoid excrescences; the muscle-coat is thickened both from the hypertrophy of the muscle-fibers and the production of interstitial fibrous tissue. The lumen is frequently dilated; ulceration is also common.

Other forms of inflammation are the **follicular**, the **phlegmonous**, the **pustular**, and the **membranous**. The phlegmonous form may be primary from the action of foreign bodies or corrosive poisons; but it may result from extension from the peri-esophageal lymph-glands, from abscess of the spine, from the cricoid cartilage, and from the stomach. When due to corrosion the necrotic mucous membrane is gradually shed as a line of demarcation is formed in which active suppuration is going on. The color and appearance of the slough vary with the character of the poison. If healing take place, marked stenosis may occur and the lumen may become gradually occluded.

Pseudomembranous esophagitis is found as a complication of variola, scarlatina, measles, typhoid, and the like; true diphtheria of the esophagus is of rare occurrence.

Progressive Changes.—Hypertrophy of the wall is due to obstruction either of the esophagus itself or the cardia of the stomach; often associated with it is dilatation of the lumen.

Tumors.—Tumors are, on the whole, not common. Metastatic growths are not known, but the tumors either originate in the esophagus or in the neighboring parts. Of benign forms may be mentioned polypoid or papillomatous fibroma, lipoma, myoma, and one case of a polypoid adenoma. Sarcoma has been observed. The most important malignant growth, however, is carcinoma; as a secondary tumor it can extend from the cardia of the stomach, pharynx, or thyroid gland.

Primary carcinoma is usually of the squamous variety, the soft glandular form being rare. We have seen one case of a glandular cancer, approximating the scirrhus type, which formed a small isolated growth and caused complete obstruction. It apparently had started from the mucous glands. The favorite sites for cancerous growths are at the point of transition of the various types of the epithelial cells and at the narrow spots in the lumen; thus, they are more frequent opposite the cricoid cartilage, at the level of the bifurcation of the trachea, and at the entrance into the stomach.

The clinical importance of carcinoma of the esophagus lies in the fact that it causes grave obstruction to the passage of food, an obstruction which is never completely relieved even when ulceration takes place. The mass may slough and extend into the neighboring tissues. Above the obstructed point there are usually marked dilatation and hypertrophy.

Tuberculosis only occurs as an accompaniment of serious tuberculous disease elsewhere. It usually is due to extension from tuberculous lymph-glands about the bifurcation of the trachea or to extension of a tuberculous ulceration of the pharynx. One form is said also to be due to the swallowing of infective sputum.

Syphilis takes the form of gummatous inflammation in the wall of the esophagus, leading to ulceration and fibrous proliferation.

Actinomycosis.—This infection is rare. Interesting instances have been described by Partsch and others, and Poncet¹ records one case in which

¹ *Bull. de l'Acad. de Méd.*, No. 15, 1896.

the process extended to the lungs and fungous clusters were found in the sputum. Extension to the organs of the chest is the rule.

Foreign Bodies and Parasites.—Among the bodies which can for a longer or shorter time obstruct the lumen of the esophagus may be mentioned bones, fish, leeches, needles, and false teeth. Hard substances may cause ulceration, leading to the formation of abscess, which may perforate into a cavity, a bronchus, or a large vessel such as the aorta. Of parasites may be mentioned thrush and trichinæ.

Alterations in Continuity and the Lumen.—**Perforation of the wall** may result from traumatism, aortic aneurysm, foreign bodies, or ulceration of malignant growths. Rupture of the esophagus is rare; it is due to extensive trauma or to excessive internal pressure. It is probable that many cases are preceded by a malacia of the wall.

Stenosis may be congenital; due to the fibrous contraction produced by swallowing corrosive liquids; to tumors, foreign bodies, or external pressure. The last mentioned may be caused by enlarged mediastinal glands, enlarged thyroid, tumors, and aneurysms.

Diverticula arise either from pressure or traction. The first variety is due to pressure from within upon a weakened muscular wall. It is not due to a single great mechanic insult, but to a succession of small ones which lead to a dissociation of the muscular fibers of the wall. These give way, and thus a hernia of the mucosa through the muscularis is the result. Diverticula *a pulsione* are most common at the junction of the pharynx and the gullet.

Traction diverticula are single or multiple and form a conic sac, situated most frequently at the level of the bifurcation of the trachea. The wall of the sac may consist of all the elements of the esophageal wall or the muscle-coat may be absent or thinned out. The tip of the cone is usually pigmented and fibrous, and a fibrous and calcareous gland is frequently attached. Most cases are thus evidently due to the adhesion and subsequent contraction of caseous lymph-glands.

THE STOMACH.

Malformations.—**Complete absence** of the stomach is found but rarely, associated with the condition of acephalus. An organ of abnormally small size is found occasionally even in otherwise well-developed persons. The pyloric orifice may be totally or, more often, partially stenosed, a condition which leads to dilatation and hypertrophy of the stomach. Owing to the formation of septa the organ may be divided into various chambers. Diverticula are rare. In the condition of transposition of the viscera the organ may be turned around, so that the pylorus is situated to the left.

Hour-glass deformity of the stomach may be congenital, due to persistence of a physiologic state of contraction, the cicatrization of an ulcer, tumors, torsion of the stomach, hernias, and to adhesion to displaced viscera (Fig. 246).

According to Bettman,¹ the cardiac orifice of the stomach is situated to the left side of the body of the tenth dorsal vertebra, and is a fixed point; the pylorus in the male lies, as a rule, on the body of the first lumbar

¹ *Phila. Monthly Med. Jour.*, March, 1899.

vertebra, about 4 to 6 cm. to the right of the median line and 6 to 8 cm. lower than the cardia; the pylorus is usually movable to the extent of 2 to 3 cm.

Occasionally the position is more vertical, recalling the embryonic condition. A cylindric shape of the pyloric half of the stomach is not infrequently seen at autopsies, due to postmortem rigidity or a functional contraction.

Dislocations of the stomach may take place through a defect of the abdominal wall or through fissure of the diaphragm, either congenital or acquired. In the latter case the organ is found in the left pleural cavity, dislocating the heart and lungs upward.

A much more common condition is that of **gastroptosis** (Glénard's disease). This is characterized anatomically by a relaxation of the gastro-hepatic and hepatopyloric ligaments, leading to a more or less pronounced descent of the pyloric portion of the stomach, whereby the viscus tends to assume a more vertical position. In a few cases the lesser curvature alone is prolapsed. The condition is generally part and parcel of a general

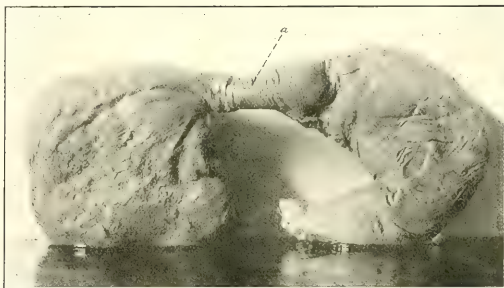


FIG. 246.—Hour-glass contraction of the stomach (from scarring); the stomach is turned inside out: *a*, linear scar.

prolapse of the abdominal viscera, particularly the transverse colon, right kidney, and the liver. With this is associated a particular symptom-complex, nervous dyspepsia and atony of the stomach, dragging sensations in the back, constipation or constipation alternating with diarrhea, anemia, and, in the latest stages, pronounced neurasthenic symptoms.

According to Glénard, enteroptosis is the anatomic basis of neurasthenia; but this view is not usually accepted. Bouveret and Charcot thought that enteroptosis was rather the result than the cause of neurasthenia, owing to a lack of muscular and nervous tone.

The causes are pressure upon the stomach from above, as from corsets, enlarged liver, or from the cramping action of a long, narrow, or phthisic chest; relaxation of the supporting ligaments, as from weakening of the abdominal walls from pregnancy, pressure by tumors and cysts, nervous depression; causes which tend to pull the stomach down, as overeating, a loaded colon, the weight of tumors, or the traction of adhesions.

Circulatory Disturbances.—The amount of blood present in the wall of the stomach varies within wide physiologic limits, and consequently

the postmortem appearances must be considered in relationship to the digestive functions at the time of death.

Edema is rare even when associated with inflammatory processes.

Anemia occurs in general anemia, and only specially in connection with parenchymatous degeneration of the mucosa.

Hyperemia, apart from the active congestion due to the action of corrosive substances or inflammation, is attributable to stasis of the blood, due either to hepatic affections and portal obstructions from whatever cause, or indirectly to cardiac or pulmonary disease. The pyloric portion is that usually affected. The veins are distorted and prominent, the mucosa is a violet-blue color, and there is not infrequently hemorrhage from diapedesis. In chronic cases there may be marked pigmentation of the mucous membrane.

Hemorrhages into the stomach-wall are common, and are dependent on increased vascular tension or disease of the vessel-walls. They are found in the hemorrhagic diathesis, leukemia, pernicious anemia, scorbutus, acute yellow atrophy of the liver, and in many acute infections; also in poisoning from phosphorus, strychnin, and morphin; and from severe vomiting. A frequent cause is the erosion of a vessel-wall from a simple or cancerous ulcer, or from the rupture of a varicose vein. When recent the blood is bright red, acid, pure or mixed with food, and may contain clots. If the hemorrhage be of some standing, the blood is altered by the action of the gastric juices and becomes of a coffee-brown color. It is hardly necessary to state that all blood vomited does not necessarily come from the stomach. It may come from the nose, mouth, or esophagus, from the lungs, or from the oozing of an aneurysm. In the case of infants, blood and pus are often swallowed in the act of nursing from a suppurating breast, and may afterward be regurgitated, sometimes giving rise to an error in diagnosis.

Retrogressive Changes.—**Simple atrophy**, whereby the mucous membrane becomes thin and the glands granular and diminished in size, occurs as a part of a general senile atrophy, in cachexia, and marasmus. Associated with this is often a diffuse or patchy fatty degeneration of the affected mucosa.

Fatty degeneration occurs also in septicemia, variola, typhoid fever, pernicious anemia, leukemia, and in poisoning by phosphorus, arsenic, lead, and other substances.

Hyaline, colloid, and amyloid degeneration are not uncommon.

A brief reference should be made to the condition of **self-digestion** of the stomach (postmortem gastromalacia). As in the case of the esophagus, we sometimes find situated on the posterior wall of the fundus, and often affecting the esophagus as well, local areas of softening which, from their appearance and special characters, are to be attributed to the digestive action of the gastric secretions. Much difference of opinion has been exhibited over the question whether or not this softening is exclusively a postmortem phenomenon. In the vast majority of cases it is due to digestive action and decomposition. In a considerable experience of autopsy-work, where the examinations were generally conducted within twenty-four hours after death, we have found the condition to be decidedly rare. The determining facts seem to be the secretory activity of the gastric mucosa at the time of death and the length of time that has elapsed since death. It is, however, quite possible that in certain diseases where the power of resistance of the

gastric mucosa is diminished the phenomenon may be an agonal one. The gross appearances are the same as those of the analogous condition found in the esophagus.

Of much more importance is the so-called **peptic ulcer** which is found both in the stomach and duodenum. In the duodenum this is not found below the bile-papilla, being confined to that portion acted on by the gastric secretion.

A typical peptic ulcer is round or oval, penetrating more or less deeply into the wall of the viscus. It has a characteristic funnel-shape, the edges being terraced and gradually narrowing as the base of the ulcer is reached. The edges are more or less sharply defined. Sometimes the edges are rounded in chronic ulcers, and the whole stomach-wall may be thickened. The ulcer is occasionally greatly pigmented owing to the action of the gastric ferment upon the blood; sometimes a number of superficial erosions tending to coalesce have been found, a fact which throws some light on the etiology of the condition.

Microscopically, a fresh ulcer shows but little. Besides the terraced appearance at the edges there may be no further noticeable change, or at most a fine granulation of the cells. Even in ulcers of long standing the inflammatory and productive changes are by no means pronounced; the muscularis shows fatty changes, there is some inflammatory infiltration with leukocytes, and the vessels show proliferating endarteritis. Only exceptionally is there a marked inflammatory reaction.

Peptic ulcers may be single or multiple, and are situated usually near the pylorus, and preferably on the lesser curvature; also in the duodenum. Their appearance may vary from that of small superficial erosions, often seen in a hemorrhagic patch, to that of a round or oval ulcer or even a large girdling ulcer. The causes are many, but seem to depend generally upon defects in the circulation of the part, due to thrombosis, embolism, or disease of the vessel-walls. Small areas of hemorrhage or anemia may lead to minute erosions of the mucosa, and ultimately to ulcer formation. The association with severe burns of the skin is well known, and the condition appears to be analogous to the necrotic changes which occur in the lymph-glands from the action of toxic substances derived from the destroyed area. Whenever erosion takes place the digestive action of the gastric juice is a potent factor in promoting a progressive ulcer formation.

The ulcers are essentially chronic, and give rise to a variety of symptoms. Repeated small hemorrhages may give rise to anemia; larger hemorrhage from an eroded vessel may lead to death. Pain after food, and dyspeptic symptoms, are often complained of, but in many cases the condition is quite latent. A serious result is perforation into the general abdominal cavity and purulent peritonitis. An ulcer on the posterior wall may perforate into the peritoneal sac, a relatively favorable event; this may lead to a fibrous perigastritis. Rarer perforations are into the colon, gall-bladder, through the abdominal wall, into the left pleural cavity, the left lung, or into the pericardial cavity. Frequently in chronic ulcers fibrous adhesions occur between the ulcer and neighboring organs, such as the pancreas, the liver, and the neighboring lymph-glands.

Finally, ulcers may heal, tending to the production of minute fibrous scars or to large stellate, contracted cicatrices. Stenosis of the pylorus is one of the results of this condition.

Progressive Changes.—**Hypertrophy** of the muscularis, generalized or limited to the pyloric region, is found in connection with chronic gastritis and tumors, while certain other cases are probably to be classed as true hypertrophies from overwork. Congenital hypertrophy of the pyloric ring in infants has been described. Local proliferations of the mucosa, leading to the formation of papillomatous or polypoid excrescences, either sessile or pedunculated, are often seen in chronic gastritis (*état mamelonné*) or at the edge of ulcers. Many of these, from their structure, may be classed with fibroma or adenoma.

Inflammations.—Our ideas on the subject of gastric inflammations are based partly upon observation and partly upon analogy, for the reason that most of these conditions, unless they be present as complications of serious disease, rarely lead to death, so that our material for study is comparatively limited. Further, postmortem changes may often mask the original condition so much that serious disease of the organ may present after death but few traces.

Inflammation of the stomach—**gastritis**—in the vast majority of cases is due to the action of irritating substances that have been ingested; some cases are also due to the action of toxic substances circulating in the blood; while a few cases are to be attributed to the extension of inflammatory processes from neighboring organs. Ingested substances act as irritants largely through their chemical or physical properties. Thus, many belong to the class of corrosives, such as sulphuric acid, nitric acid, caustic potash, sublimate, carbolic acid, and the like; others are pus and sputum. Many food-stuffs may on occasion act as irritants. An excessive amount of food, owing to the inability of the stomach to digest it and eliminate it quickly enough, is a frequent cause; particularly when the stomach is impaired from, for instance, muscular atony, pyloric stenosis, cancer, or fibrous induration, these causes act with greater intensity. Should, for any of these reasons, food be retained and subjected to abnormal fermentation, putrid gases, irritating fatty acids, and bacterial toxins are produced in considerable amount and lead to severe disturbances.

Hematogenous affections occur particularly in the course of infections and intoxications, as in septicopyemia, typhoid fever, ulcerative pulmonary tuberculosis and variola. Metastatic abscess formation appears, however, to be rare.

Gastritis from extension can occur from any localized inflammatory process in the neighborhood of the stomach. Perforation occurs; or there may be fistulous communication with other organs. Among the causes which may be mentioned are cholelithiasis and empyema of the gall-bladder, and suppurative pancreatitis. A perinephritic abscess has been known to rupture into the stomach. In a probably unique case recorded by the writer,¹ the patient vomited broken-down pus and blood three days before death.

The most severe condition is brought about by the action of corrosives, the appearance presented varying according to the strength and character of the destructive fluid and the length of time that has elapsed since its ingestion. When strong acids have been used, extensive necrosis of the mucosa is the result. The slough produced by H_2SO_4 is hard, dry, brittle, and of a grayish color; HNO_3 and HCl produce a yellow color; caustic potash produces a transparent, pulpy, digested appearance. In the portions

¹ *Montreal Med. Jour.*, Feb., 1898.

less affected are seen signs of a more or less intense inflammation, often hemorrhagic.

Simple acute catarrhal gastritis, as might be expected, only rarely meets the eye of the pathologist, except as a complicating condition, since it does not lead to death. Our knowledge of the finer details is gained, therefore, largely from experiment.

Catarrhal gastritis is characterized by hyperemia and swelling of the mucous membrane, together with an increased production of an adherent viscid exudate consisting of mucus, degenerated epithelium, and leukocytes. Here and there small hemorrhages may be seen, together with superficial erosions. Microscopically the secretory cells of the glands are seen to contain an excess of mucin, and are desquamating. The epithelium of the peptic glands is more granular than usual, and is often detached from the basement membrane. The interstitial blood-vessels are distended, and there is a round-cell infiltration between the lobules and in the submucosa. The endothelium of the lymphatics also may show signs of proliferation. These changes are usually confined to the pyloric region, but may be generalized.

A more severe but somewhat rare affection is **pseudomembranous gastritis**. In its typical form it is found most frequently in children. In mild forms the membrane lies in small patches upon the top of the rugæ, but only rarely is the whole interior of the stomach covered by a uniform layer, forming, as it were, a cast of the organ. The membrane is grayish or sometimes, from blood staining, brownish in color, and is loosely attached to the mucosa. The underlying mucous membrane is generally hyperemic and greatly swollen, with hemorrhagic patches.

The condition occurs most commonly in newborn children from septic infection of the umbilical cord, in diphtheria, scarlatina, measles, and variola, but rarely in other infectious fevers. A true diphtheria of the stomach does occur, and, curiously enough, the infection may pass from the throat to the stomach without affecting the esophagus. Suppuration and necrosis lead often to a more or less extensive loss of substance in the mucosa, and deeply eroding ulcers may be the result.

Phlegmonous gastritis occurs rarely as an idiopathic affection, particularly in drunkards, but sometimes is found in general pyemia.

A rare form of gastritis, the **follicular** form, is due to inflammation of the lymph-nodes, which are present in small numbers in the stomach. When suppuration takes place small follicular ulcers are produced.

Chronic catarrhal gastritis presents a variety of forms, though these are to be regarded as stages in one and the same process. In this condition the mucosa is of brown or grayish-brown color, due to an iron-containing pigment derived from the blood, which is situated in the interglandular tissue and also in the secreting cells. Congestion, apart from cases complicated by passive hyperemia of systemic origin, may be, in the later stages at least, completely lacking; the mucosa is covered by a thick, adherent layer of mucus mixed with leukocytes and more or less altered epithelial and glandular cells.

Microscopically, the most important change is a cellular infiltration in the interstitial tissue, chiefly in the superficial layers of the mucosa; this leads to wider separation of the glandular elements. The secreting ducts are catarrhal, often dilated or cystic and tortuous, the lining cells showing

evidence of an increase both in size and numbers. These changes lead to a thickening of the entire mucous membrane with a granular appearance.

In some cases the interglandular proliferation is so great that warty or polypoid projections are the result, either at the pyloric end or scattered over the whole organ—*gastritis polyposa*. In another class of cases the productive change is most marked in the glandular elements, so that out-growths resembling adenomas are produced. These last two varieties are classed together under the name *hypertrophic gastritis*.

A further type, **atrophic gastritis**, is due to the production of an interstitial connective tissue in the mucosa, leading to sclerosis and contraction of the organ. The mucosa in this case is grayish in color, hard, and thin. The other coats may also show extensive fibrous proliferation, so that the total thickness of the stomach-wall is increased while its capacity is lessened.

Chronic gastritis is found frequently in drunkards, in long-standing passive congestion, and as a secondary manifestation in gastric ulcer, carcinoma, or dilatation of the stomach.

Of the **specific infections**, the **tuberculous**, **typhoid**, and **syphilitic** are the only ones of note. They are all rare. The mucosa of the stomach, possibly owing to the character of its secretion, does not afford a suitable medium for the growth of pathogenic germs. Complete immunity of the stomach, however, does not exist.

Orth, in an experimental study in which he fed rabbits upon tuberculous material, produced typical lesions in the intestines in 7 cases and in the stomach in 1.

Alice Hamilton¹ records 3 cases of tuberculous ulceration of the stomach, and has collected 16 more which were beyond cavil. The ulcers are generally multiple and situated in the neighborhood of the pylorus. Some present little more than superficial erosions of the mucosa, in which only the discovery of the bacillus can determine their true nature; while others have a more typical appearance, with infiltrated edges, and an irregular base containing caseous tubercles.

Tuberculous ulceration of the stomach is invariably associated with advanced tuberculosis elsewhere, generally pulmonary. Hamilton thinks that some of the cases are due to the production of small erosions of the mucosa from hemorrhage, which subsequently become invaded by bacilli from the sputum. It is striking that in many cases the intestines were free from tuberculous lesions.

Typhoid ulcers are recorded, but are still rarer than tuberculous ulcers.

Syphilitic gummas of the stomach-wall are rare, and may lead to ulceration or fibrous scarring.

Actinomycosis of the stomach is rare.

Tumors.—**Lipoma** and **myoma** are rare and of little importance; **sarcomas** are also rare.

Very common are **carcinomas** originating usually in the glandular elements of the mucous membrane. They may arise from an apparently healthy mucosa or from the base of an old peptic ulcer. They gradually infiltrate through all the coats of the stomach and reach the periportal and retroperitoneal glands, the omentum, liver, and frequently the lungs. Some few cases are possibly to be regarded as cancerous metaplasia of an accessory

¹ *Bull. Johns Hopkins Hosp.*, viii., 75, 1897.

pancreas situated in the stomach-wall. Carcinoma is usually situated at the pyloric extremity and the lesser curvature, but occasionally at the fundus or cardia. The condition is often characterized by pronounced ulceration of the mass, which indeed may be so great that the whole carcinomatous tissue sloughs away, leaving its character only to be inferred from the presence of metastases.

There are five main varieties of gastric carcinoma: the **medullary**, the **adenocarcinoma**, the **scirrhus**, the **colloid**, and the **squamous**.

The first form produces a spongy, soft, nodular mass, generally in the pyloric region; it is characterized microscopically by abundant masses of cancer-cells with little connective tissue. Fibrous induration of the stomach-wall is a frequent accompaniment.

The adenocarcinoma forms large, soft, nodular masses, having a fungous or shreddy appearance, and is recognized microscopically by the formation of atypical glandular processes; the stroma is small and often infiltrated with small cells.

The scirrhus cancer is found at the pyloric portion or affecting the organ as a whole. The wall of the stomach is thickened considerably, and the wall of its cavity contracted, so that in extreme cases the viscus may scarcely contain a teacupful. The mucosa is sometimes preserved above the mass, but is frequently absent. Fibrous induration of the muscularis is a marked feature.

Colloid cancer forms nodular masses, or a diffuse infiltration of the stomach-wall. Both the cancer-nests and the connective tissue show the gelatinous degeneration.

Squamous epithelioma is somewhat rare. It is found at the cardia, and probably arises from the lower extremity of the esophagus, whence it invades the stomach.

Parasites and Abnormal Contents.—Any of the usual intestinal parasites may find a lodgement in the stomach-cavity. The **Pentastomum denticulatum** and the **echinococcus** are sometimes, though rarely, present in the stomach-walls or gain an entrance from some neighboring organ.

Thrush is occasionally present in small, isolated, whitish patches on the mucous membrane when the fauces are extensively involved. In cases of dilatation through retention of the food and altered secretion, offensive gases, fatty acids, and other abnormal products of fermentation are produced, together with the development of yeast-fungi, sarcinae, and bacteria; yet it should be said that at no time are micro-organisms relatively abundant.

Very frequent are **foreign bodies**, which get into the stomach with the food or are swallowed accidentally. Buttons, needles, spoons, scissors, and many other substances have been swallowed by hysteric patients or circus performers, and may at times give rise to serious trouble. Hair-balls, composed of felted hair, the accumulation of months, and matted into a compact mass by the muscular action of the stomach, are frequently found in cattle and occasionally in human beings. Schopf¹ has collected 16 such cases, and recorded 1 in which the mass formed a complete cast of the stomach and duodenum, weighing 5 ounces.

¹ *Wien. klin. Woch.*, Nov. 16, 1899.

THE INTESTINES.

The pathologic manifestations found in the intestines bear a general resemblance to those of the stomach, but there are several peculiarities in structure that have an important bearing upon the causation and the character of the disease-processes and distinguish them in certain particulars from those of the stomach. One of these is the condition of the peritoneal folds which allows of considerable mobility of certain portions of the intestinal tract, thus facilitating the production of important conditions, such as hernia, constrictions of the bowel-lumen, inflammatory adhesions, and the like. Another point of difference is the presence of villi with chyle-vessels which end blindly toward the lumen of the bowel, but form a freely anastomosing network in the mesentery. These play an important role in the extension of infection to the neighboring parts, and obstruction of their channels leads to characteristic appearances.

A further important anatomic condition is the presence of lymphoid nodules, which in the stomach are few and unimportant, but in the intestines are much in evidence and afford one of the most ready points of entrance for infective agents and toxins.

Malformations.—Total **absence** of the intestines and such like gross defects are found only in connection with other serious malformations. Inverted positions of the various portions are recorded both with and without associated inversion of the other abdominal or thoracic viscera. Hernial protrusions may take place through a fissure of the abdominal wall or a defect in the diaphragm. An abnormal course of the colon is common. This consists of a V-shaped downward loop, or accessory loops may be formed. Such are found in about 9.5 per cent. of postmortems.

Very frequent are **defects** of the lower portion of the bowel and the urogenital sinus. A cloacum may be found in which the bladder and the rectum discharge. In this condition the bladder may be divided and the large intestine absent, so that the ileum empties into the bladder. In less-pronounced cases there may be merely incomplete closure of the septum between the rectum and the urogenital sinus. Associated with this is imperforate anus, a condition of great practical importance. In such cases the rectum may end as a blind pouch or discharge into the bladder, urethra, vagina, or perineum.

A frequent condition is the so-called **Meckel's diverticulum**, present in our experience in 2 per cent. of autopsies. This is a condition found usually in the ileum, not more than one meter above the ileocecal valve. It consists of a cylindric diverticulum which may be somewhat dilated at the free end, or sometimes of a funnel-shape. It is situated away from the mesenteric attachment. The diverticulum represents the remains of the omphalomesenteric duct, and may be connected with the umbilicus or some other part of the abdominal wall by a fibrous band. It consists structurally of all the coats of the intestine, though the muscular wall may be thinned at the apex. It may have a free communication with the lumen of the bowel or be shut off partially by a valve. It derives its importance from the fact that coils of intestines occasionally become caught and strangulated in cases in which the fibrous attachment persists. In some cases a small portion of the original duct is pinched off at the umbilicus, forming a cyst or solid tumor, sometimes called an adenoma. In other cases diverticula become more or less

completely shut off from the intestinal lumen, and so form cystic tumors, the so-called enterocystomas, which are filled with fluid.

Congenital dilatation and stenosis of the intestines are not rare. Idiopathic dilatation of the colon, congenital and acquired, has attracted some attention recently; C. F. Martin,¹ has recorded 1 case, and collects 13 others of presumably congenital origin. Acquired cases are much more common. The condition is invariably fatal. In the acquired cases constipation plays an important role, and many cases are found among the insane.

Partial or complete defect in the formation of the appendix vermiformis is found.

A remarkable condition is the presence of an accessory pancreas² in the intestinal wall, which may afford an explanation for the development of certain tumors.

Acquired Abnormities of Form and Position.—A **hernia** or rupture may be defined as the condition in which one or more viscera become dislocated from the normal position and either appear externally or remain concealed in some recess of the body-cavity. Here we are dealing more particularly with hernias of the intestines. Hernias may, then, be external or internal.

In the case of an external rupture, a portion of the intestinal tract finds its way through some passage, either physiologic or pathologic, and makes its appearance beneath the skin and subcutaneous tissues. Generally the intestine carries before it a prolongation of the peritoneum. This is only absent in cases in which the membrane is torn or when portions of the intestine, like the cecum, which are extraperitoneally situated, are prolapsed through an opening in the fascia and muscles of the abdomen.

In the early stage the sac is merely a shallow concavity, but later becomes more globular or pear-shaped, communicating with the abdominal cavity by a narrow neck.

The contents of the hernial sac are various. Most frequently they are the small intestine, the mesentery, and great omentum; less often the cecum and large intestine, or some of the other abdominal viscera, such as the stomach, liver, ovary, and urinary bladder.

When only a small portion of the side of the intestinal canal is caught in the sac, it is called a Littré hernia. Such can give rise to the same symptoms of obstruction as the more usual type. Some hernias are greatly assisted by the presence of a pre-existing sac, such as, for instance, congenital patency of the inguinal canal. In other cases a tumor or local adhesion may exercise traction upon the peritoneum and produce a sacculated condition.

The chief causes of hernia production are to be found either in an acquired lack of support of the peritoneal membrane at some particular point, usually the various foramina of the body, or a congenital patency of certain canals which are usually closed, together with some internal pressure brought about by strain or by the weight of the contained viscera.

We can recognize the following forms:

External Hernias.—*Inguinal hernias* are the most frequent, particularly in men. They are brought about by congenital patency of the inguinal canal or prolapse of the intestines with the peritoneal sac through the canal.

¹ *Montreal Med. Jour.*, March, 1897.

² See Nicholls, *Montreal Med. Jour.*, Dec., 1900.

According as they lie in the inner or the outer side of the epigastric artery, they are divided into internal and external inguinal hernias.

Femoral hernia is also frequent, especially in women, and is produced at the femoral ring by prolapse of the intestines beneath Poupart's ligament along the course of the femoral vessels.

Obturator hernia, at the obturator foramen along the course of the obturator artery and nerve. It is not frequent.

Ischiadic hernia, at the ischiadic notch.

Perineal hernia, between the bundles of the levator ani muscle.

Umbilical hernia is most frequent in women who have borne children, but is also congenital; prolapse takes place through the umbilical ring or into the strands of the umbilical cord. It may be large, and usually contains intestine with a part of the great omentum.

Abdominal hernia is brought about by separation of the recti muscle, as from childbearing, or occasionally results from cutting operations upon the abdominal wall.

Internal Hernias.—These are produced by prolapse of the viscera into pockets of the peritoneal sac either in the abdomen or the pleural cavity. To the first class belong the following: The bursa omentalis, which is bounded by the stomach, pancreas, liver, and spleen, and which connects with the greater peritoneal cavity through the foramen of Winslow; the fossa duodenojejunalis; the subcecal fossa; and the fossa intersigmoidea. Coils of intestines can become prolapsed in all these. The fossa duodenojejunalis can contain the whole of the small intestine (retroperitoneal hernia).

Diaphragmatic hernia is produced by congenital defects in the diaphragm or tears resulting from traumatism and stab wounds. The stomach, intestines, and kidney have been found in the thoracic cavity in such cases.

If the hernia has lasted any length of time, secondary changes set in, chiefly of a chronic inflammatory or mechanic nature. The hernial sac becomes thickened and its constituent elements fuse together, so that the original layers can no longer be distinguished. Its inner surface is smooth and pearly, often with elevated ridges traversing it. The various coils of intestine or the mesentery may be adherent to each other or to the hernial sac by firm fibrous adhesions. The mesentery is often shortened and scarred from inflammatory thickening. Acute infection is liable to occur.

The condition does not tend to heal spontaneously, but generally becomes more extreme. The mobility of the coils of intestine becomes gradually more hampered, adhesions set in, the neck of the sac becomes contracted, and finally what was once a reducible hernia becomes irreducible. When the mobility is so much impaired that the intestinal contents can no longer be passed on and severe circulatory disturbances set in, the condition is spoken of as "incarceration."

An overdistention of certain of the coils with feces may cause pressure upon the others, and thus precipitate the condition. Pressure may also be exerted through the elasticity of the tissues about the neck of the sac.

If the pressure becomes so great that the venous return is hindered, the intestine becomes greatly congested. Edema and hemorrhages may be produced, so that the coils become swollen or of a purplish color, though they may still retain their luster. If the condition is not relieved, the hernial contents become greatly inflamed, and eventually gangrenous. The intestine is of an intense blackish or bluish red, with possibly perforations or

suppurative foci here and there. At the site of the constriction the tissues are of a paler grayish-white color. This condition is called "strangulation."

Intestinal obstruction, apart from hernia, is caused by strangulation, volvulus, intussusception, strictures, tumors, and abnormal contents.

In 1134 cases of intestinal obstruction analyzed by Leichtenstern, 35 per cent. were from **strangulation**. Fibrous adhesions from old peritonitis may cut off pockets from the general peritoneal cavity or form loops through which portions of the intestine can become prolapsed. From subsequent distention or from peristaltic action these may become kinked and obstruction ensue. A similar condition can be produced by slits in the mesentery or great omentum. The most frequent causes, however, are peritoneal adhesions and adherent Meckel's diverticulum.

Intussusception or Invagination.—This is comparatively frequent; 34 per cent. of the cases occur in children under the age of one year. In this affection one portion of the bowel slips into another. The condition is nearly always a descending one, in contradistinction to the postmortem invaginations, which are often ascending ones.

Various grades exist, and as the condition proceeds the inner and middle layers increase at the expense of the outer layer. In the mass thus produced three layers of bowel are recognizable: An outermost or intussusciptens or receiving layer; an innermost or entering layer; and a middle or returning layer.

The following varieties have been found: The ileocecal, in which the ileocecal valve passes down into the colon; the ileocolic, in which a portion of the ileum passes through the valve; the ileal, affecting the ileum alone; the colic, in which the colon is alone involved; and the colicorectal, affecting the colon and rectum. Irregular peristalsis is probably the cause.

The portion involved forms a sausage-like tumor with a curved outline. In the early stage there is only slight reddening, with perhaps a little plastic exudate; but in more advanced cases in which the mesentery has been caught, the parts are greatly swollen and congested, the layers are glued together by inflammatory material, and the intussusception can no longer be reduced. Finally, necrosis and gangrene may result; the patient usually dies of shock or peritonitis. A much more uncommon event is sloughing of the strangulated portion, with union of the two ends and complete healing. In the Pathologic Museum of McGill University are 17 inches of small intestine passed per anum by a boy who had symptoms of strangulation, and who completely recovered.

Volvulus is most frequent between the ages of thirty and forty. The twist occurs about the axis of the bowel; the lumen of the bowel is obstructed and the circulation in the mesentery interfered with. Fifty per cent. of the cases occur in the sigmoid flexure. The next most common site is about the cecum. Volvulus occurs in the movable portion of the intestine, and is supposed to be brought about by peristalsis caused by unequal filling of the coils of the intestine or through contusions. An abnormally long mesentery is supposed to contribute.

Strictures and tumors seldom cause acute trouble, but are frequent causes of chronic obstruction.

Stenosis of the bowel-lumen can occur from fibrous inflammation in the wall of the intestine itself, as occurs from tuberculosis, syphilis, dysentery, or uremic ulceration; congenital stricture; new growth, most commonly the

cylindric-cell carcinoma of the rectum ; compression or traction from without, as from tumors, a coil of intestine loaded with feces, or healing peritonitis.

Among **foreign bodies** which may cause obstruction may be mentioned gall-stones, fecal accumulations, enteroliths, masses of hair, false teeth, fruit-stones, round worms, and medicinal substances, such as magnesia and bismuth.

The symptoms produced by intestinal obstruction, whether from hernia or any other cause, are characteristic. The three most important are constipation, pain in the abdomen, and vomiting. The vomiting is at first gastric, then bilious, and finally stercoraceous. If the obstruction is not high up, distention of the abdomen usually occurs. The face is pale and anxious, and the patient finally becomes collapsed. A metastatic pneumonia, due to the *B. coli*, is not an infrequent complication.

Acquired diverticula¹ of the intestine are not uncommon. Unlike the true diverticula, of which Meckel's is the type, they are usually composed of only one or two of the coats of the bowel, the muscular coat often being absent. In many cases the condition is really a hernia of the mucosa into the serosa. In other instances the serosa is the only constituent. The sac is usually situated between the layers of the mesentery or colon alongside of it. Many cases are associated with ulceration of the mucosa or are due to severe coughing. Hansemann² has recorded a case in which there were 400 diverticula, varying in size from that of a hemp seed to that of a pigeon's egg. These were really hernial protrusions of the mucosa into the sheaths of the mesenteric veins. After middle life there seems to be a physiologic tendency to weakening at these points (Fig. 247).

Circulatory Disturbances.—Vascular disturbances are common, but the postmortem appearances are rarely, if ever, striking.

Edema is due to active or passive congestion, acute and chronic inflammations, peritonitis, or is part of a general anasarca. The walls of the intestine are swollen, resembling wash-leather, the muscular part being pale and gelatinous. The mucosa is swollen, pale, and has a watery, sodden appearance. The natural folds are accentuated.

Active hyperemia gives rise to marked reddening of the mucosa. It is generally caused by irritating intestinal contents or dilatation of blood-vessels under the action of nervous stimuli.

Passive hyperemia occurs from obstruction in the course of the general circulation as well as from hepatic cirrhosis or other interference with the portal circulation. Local passive hyperemia is seen in the compression of the veins seen in the condition of hernia and strangulation. Varices occur occasionally. The most important point is the production of *hemorrhoids*, due



FIG. 247.—False or acquired diverticula of the ileum.

¹ Fischer, *Jour. of Exper. Med.*, vol. v., 1901.

² *Virch. Archiv.*, cxliv., 400, 1896.

in part to stasis in the inferior hemorrhoidal vein. The condition is evidenced by varicosities of the veins within the rectum or appearing externally about the anus in the form of small globular swellings. Among the causes may be mentioned sedentary habits, chronic constipation, pressure of tumors or the pregnant uterus in the pelvis, or obstruction to the portal circulation. The piles are apt to become inflamed and ulcerated and may give rise to hemorrhage. Repeated loss of blood in small amounts in this way is sometimes the cause of severe anemia, the reason for which is often overlooked.

Hemorrhages occur in active and passive congestion, and are seen most frequently in the mucous membrane. They are a frequent accompaniment of various inflammatory affections, such as dysentery, and especially typhoid fever, as the result of ulceration. Small hemorrhages are recorded in pernicious anemia and hemophilia.

Embolism or thrombosis of the superior mesenteric artery may lead to hemorrhagic infarction of the whole intestinal wall.

Frequently over the ecchymosed area the mucosa shows a superficial loss of substance. After the blood has been outpoured for some time it becomes changed into a blackish dirty mass, owing to the action of the sulphuretted hydrogen in the feces.

Progressive Changes.—The hypertrophic and regenerative disorders of the intestines bear a great resemblance to those of the stomach.

Hypertrophy of the bowel-wall is frequently seen in cases of congenital or acquired atresia of the lumen, extending for some distance above the point of obstruction. It is due to the increased demand put upon the muscular fibers; it is often associated with dilatation. Which element predominates, hypertrophy or dilatation, depends upon whether the atresia is brought about slowly or rapidly; hypertrophy takes time to develop.

Apart, however, from the forms of purely mechanic origin there are others into which other factors enter. Such are the hypertrophy seen in association with chronic inflammation and tumors. Strictly speaking, these are not to be regarded as examples of pure hypertrophy, for the thickening of the muscular wall is brought about largely by the production of fibrous tissue or an infiltration with new growth.

Hyperplasia of the mucous membrane is seen in association with chronic catarrhs and the various forms of chronic ulceration (uremic, dysenteric, tuberculous). Thus, small elevations or polyps are produced, composed largely of glandular elements. Similar outgrowths are seen in young children, apparently unconnected with previous inflammatory disturbance. They may be rounded or lobulated, and may depend from a narrow pedicle. If situated near the anus, they may prolapse and bring down with them the mucous membrane of the rectum.

The glandular elements usually show their normal relationship, but often undergo a quantitative hypertrophy. The gland-tubes become lengthened and dilated, often branched and wavy, and many show cystic dilatation.

These are classed better perhaps with the adenomas, and may form quite large papillomatous-looking outgrowths (Fig. 248). They are important, as they may form the starting point of carcinoma.

Inflammations.—The inflammatory disturbances found in the intestines present, on the whole, great similarity to those of the stomach, both pathologically and etiologically. Any differences are probably to be explained by differences in physiologic function and mechanical conditions.

The great majority of inflammations arise from the irritative action of the intestinal contents, which may have undergone abnormal fermentation or may contain toxic substances of animal, vegetable, or mineral origin, or again from the activity of various pathogenic bacteria. Some cases, however, arise from infectious or toxic substances carried to the intestine through the blood and body-juices. These act probably by depressing the specific tissue-cells of the parts, modifying secretions, and by increasing the virulence and infecting power of certain micro-organisms contained in the feces, which under ordinary circumstances are nonpathogenic.

Many forms of inflammation are associated with an abundant outpouring of fluid into the lumen of the intestine. But not all such fluid should be regarded as inflammatory exudate, for the amount of succus entericus can be considerably increased under vigorous stimulation or violent peristaltic movement.

The portions of the bowel most apt to be affected are the duodenum, owing to its direct association with the stomach, and the large intestine, which is liable to irritation from the accumulation of feces within it.

Inflammation of the intestine is spoken of in general as *enteritis*, but it is rare for the whole tract to be affected at once, so that various subvarieties are recognized—duodenitis, ileitis, colitis, proctitis, etc.

Simple acute catarrh is characterized by a hyperemia of the mucosa of varying degree. The postmortem appearances are not constant, for a very considerable amount of catarrhal inflammation can exist without producing effects which are recognizable after death. In some cases there is a patchy reddening of the mucosa, about the lymph-vessels, and on the tops of the rugae, and in severe cases in the serosa itself; occasionally punctate ecchymoses are seen. The mucosa is usually swollen, so that the folds are more prominent than normal, and it has a dull, cloudy, grayish appearance. Generally, though not invariably, the mucosa is covered with a mucous or serous exudate containing relatively few leukocytes. In other cases the leukocytes are more abundant, so that the exudate has a purulent or mucopurulent character. Frequently the exudate is mixed with desquamated epithelial cells in varying stages of degeneration; this is frequently a post-mortem manifestation.

Microscopically the mucosa and submucosa show marked hyperemia with some edema. The surface of the mucosa shows more or less exudate, and the secreting cells of the tubular glands show increased mucus production. Slight erosions of the mucosa may occur. In the more severe cases collections of inflammatory leukocytes may be seen in the mucosa about the gland-tubes and in the submucosa grouped around the blood-vessels.

In suppurative cases the condition is more extreme, and considerable portions of the mucosa may slough away, leaving sharply defined ulcers with infiltrated walls. The submucosa is usually markedly infiltrated with leukocytes. In some cases localized abscesses form in the submucosa, which burst into the lumen, leaving small cavities. In still other cases there is a diffuse phlegmonous infiltration.

In the so-called **desquamative enteritis** the cast-off cells form a tubular cast of the intestine. This is usually found in the large bowel, and has been described in connection with the summer diarrheas of children.

Under the term **membranous enteritis** are classed those severer forms of inflammation which lead to coagulation necrosis, with ulceration—diph-

theritic ; or to the formation of a croupous or fibrinous exudate upon the mucous membrane—pseudomembranous inflammation. It is impossible to separate these processes sharply one from another, since they are produced by the same causes, and the croupous form may pass imperceptibly into the diphtheritic.

Membranous enteritis begins probably as an ordinary catarrh with hyperemia and swelling of the mucosa, but soon passes into the severer form. The mucosa becomes red, and a brawny sort of film of a whitish-gray color appears upon the surface, particularly upon the tops of the rugæ. At first this skin can be scraped off with the knife, but sooner or later this is impossible, since a portion of the intestinal wall actually undergoes a form of coagulation necrosis. As the condition progresses the redness and swelling of the mucosa increase, the patches tend to coalesce, and the membrane, through contact with the feces, assumes a dirty yellowish-green or brown color.

The localization of the membrane upon the tips of the rugæ is characteristic. In places where the membrane is cut off shallow ulcers are produced, which may coalesce and reach a considerable size. In very severe cases the muscularis may be laid bare, and even proliferation may occur. When the lymphoid follicles are chiefly affected, ulcers not unlike those of typhoid are produced.

In the various forms of enteritis the part played by the solitary and agminated glands is a varying one. In many cases the glands show no marked change, but in others they are so greatly affected that the disorder merits the name of **follicular enteritis**.

It is somewhat difficult to say, when the glands are enlarged, how far this is a physiologic condition or a manifestation of the so-called lymphatic habit ; but there are undoubtedly many cases which are due to the various infections or intoxications.

The glands are swollen and project somewhat above the general surface of the mucosa ; they are of a grayish or grayish-white color and often surrounded by a hyperemic zone.

When Peyer's glands are similarly affected owing to the unequal swelling of the lymphoid and connective-tissue elements, the surface becomes somewhat reticulated or traversed by shallow grooves. Apart from the specific forms, typhoidal and tuberculous, follicular enteritis is particularly common in diphtheria.

Microscopically the swelling of the follicles is seen to be due to hyperemia and proliferation of the lymphoid elements. The neighboring lymph-channels are filled with cells, and in addition there may be seen a perifollicular cellular infiltration ; the follicles themselves often show no further change, but in certain cases present necrotic changes.

In advanced stages the condition may go on to suppuration, so that small follicular abscesses are produced.

Under the term **dysentery** are included a variety of different conditions which are to be referred to the activity of micro-organisms. A variety of germs have been described, but it is probable that no one particular organism is to be regarded as specific. In fact, it is certain that several distinct infectious processes are grouped under the one head, and it is likely that the dysenteries occurring in different countries are due to different etiologic factors.

Dysentery occurs epidemically, endemically, but also sporadically, as an affection of the bowels with acute onset, characterized by severe diarrhea and tenesmus. The stools may be frequent and differ much in character.

In the **acute catarrhal** form the stools may vary from 15 to 200 in the twenty-four hours. At first they are composed of clear mucus and blood, with small fecal scybala; later they are purely mucinous and bloody. At the end of about a week the blood is lessened in amount, the mucin becomes more opaque, and brownish or greenish shreddy material is present.

Tropical dysentery is the form found in most hot countries, but is met with occasionally in the temperate zone. It is usually epidemic and very fatal. One main form is characterized by intermittent diarrhea and by the presence in the stools of the *Amœba coli* (Lösch, Councilman, and Lafleur), which is now generally admitted to be the cause of the disease. The ameba is a unicellular protoplasmic mass about 15 to 30 μ in diameter, containing a nucleus and one or more vacuoles. It should be noted that there are several varieties of ameba found in the dysenteries of various countries, so that there are several subtypes. Amebæ have also been found in the stools of healthy people. Several observers have noted a form of amebic dysentery in New York and elsewhere in those who had never lived in tropical countries.

The lesions are found in the large intestine and occasionally in the lower part of the ileum. The mucous membrane is generally edematous, swollen, and hyperemic, and there are local infiltrations which show themselves as hemispheric elevations above the general surface. Ultimately the mucous membrane becomes necrotic and sloughs away, leaving an ulcer with infiltrated, undermined edges. The base is formed of infiltrated submucosa having a grayish-yellow, gelatinous appearance. Often the sloughy surface is small compared with the amount of softening that occurs in the submucosa, so that there is a small sinus formed. In other cases the ulcers coalesce, leaving sinuous tracts bridged by strands of fairly healthy mucosa. In advanced cases the ulceration may extend to the serous coat of the bowel and the whole intestine may be much thickened.

Microscopically there is singularly little leukocytic infiltration, but there is proliferation of connective tissue. Amebæ are found in the tissues at the base and edges of the ulcers, in the lymphatic channels, and sometimes in the blood-vessels.

The stools are at first frequent, bloody, and mucoid, but later are fluid and of a greenish-gray color, with some mucin. Amebæ are found in the dejections. There are apt to be focal necroses in the liver, and also abscesses which are single or multiple. Rupture of abscesses of the liver into the lung is not infrequent.

Many investigators have sought for the cause of tropical dysentery in bacterial activity. Shiga, in 1897, in an epidemic in Japan, isolated a bacillus culturally and biologically related to the *B. typhi*, which is accepted by many leading authorities as the specific cause of at least one great group of cases.¹

Diphtheritic dysentery may occur as a complication of both the foregoing varieties, but also as a primary disease. In the milder forms the tips of the rugæ are covered by a thin yellow exudate; in the severer forms the walls of the colon are greatly thickened and infiltrated, and there is exten-

¹ See Flexner, *Phila. Med. Jour.*, 1900.

sive necrosis of the mucosa, so that it may appear as a dirty-black friable mass.

Diphtheritic dysentery may also occur as a terminal event in many acute and chronic affections. According to Bristowe, it is frequent in pneumonia. In Bright's disease uremic ulcers are occasionally found, which are often of large size and may penetrate deeply, even leading to perforation and local adhesions. As the process is often a chronic one, the bowel is usually much thickened and the mucosa polypoid.

The milder forms of enteritis may heal; the inflammatory exudate is absorbed, and the destroyed glandular elements are reproduced by proliferation of the cells of the crypts of Lieberkühn. In the chronic forms, however, very striking changes ensue.

The restoration of the lost mucosa may be an imperfect one, so that there is a local atrophy of the mucous lining.

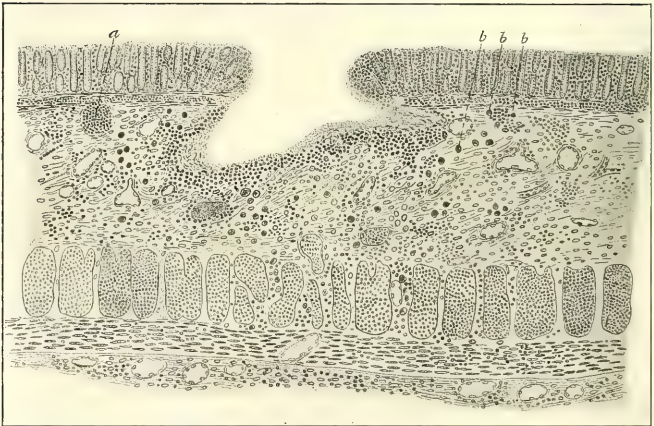


FIG. 248.—Section showing slightly excavated ulcer which extends only a short distance into the submucosa: *a*, solitary follicle; *b*, amebæ (Councilman and Lafleur).

In severe cases the mucous membrane may be permanently destroyed in places, and the floor of the ulcer is covered by connective tissue, which is derived from the submucosa. In some cases the muscle-coats are also fibrous, and, owing to the subsequent contraction, stenosis of the bowel may result.

Often in the neighborhood of chronic ulcers the mucous membrane forms polypoid or wart-like excrescences—chronic fungating enteritis. These are composed of regenerating glandular elements together with proliferating connective tissue. The glandular elements grow rapidly, so that the ducts become wavy, branched, or elongated, and owing to fibrous contraction may in parts be converted into small cysts.

Inflammation of Special Regions.—**Duodenitis** usually is part and parcel of a coexisting gastritis; it is practically of importance, since

infection may spread up the common bile-duct and the pancreatic duct. This may lead to catarrh of the ducts involved, thus predisposing to the formation of calculi; catarrhal jaundice is due to a plug of mucus in the diverticulum of Vater.

Duodenitis not infrequently leads to an acute interstitial hepatitis, and its importance in relation to acute suppurative pancreatitis will be referred to later.

Duodenal ulcer occurs under the same conditions as does gastric ulcer.

Colitis is oftenest due to a pressure-necrosis from the accumulation of hard feces. In such cases the colon is dilated and presents pockets or diverticula in which the scybala lie; at the bottom of these is frequently an ulcer. Colitis is, however, also seen in cases of generalized infection.

Proctitis, or inflammation of the rectum, is frequently brought about by various forms of traumatism, impacted feces, fish-bones, and ulceration of dilated hemorrhoidal veins. Ulceration is commonly of a chronic type, associated with thickening of the wall, more or less atresia, and polypoid outgrowths.

The ulceration may spread so that perforation of the rectum takes place, with the production of a periproctal abscess, or even partial or complete fistulæ. Such fistulæ may be rectovesical or rectovaginal. Similar conditions are produced by syphilis, tuberculosis, and dysentery.

Appendicitis.—Until comparatively recent years the affections that we now recognize as due to an inflamed appendix were classed under the terms typhlitis, perityphlitis, or paratyphlitis; or, more vaguely still, "inflammation of the bowels"; and it is largely due to American surgeons that the real origin of these cases has been worked out. It is now practically admitted by clinicians and pathologists, in English-speaking countries at least, that the vast majority of typhlitis cases are to be attributed to a diseased appendix.

With regard to etiology: appendicitis is much more common in males than in females; most cases come to operation between the ages of twenty and thirty; but where previous attacks have occurred they have frequently taken place between the ages of ten and twenty.

There are several reasons why the vermiform process is particularly liable to disease. It is a relic of what was probably a large cecal pouch, and there is considerable evidence adduced to show that it is gradually involuting. In 400 appendices obtained at postmortems, Ribbert found that 25 per cent. showed evidence of retrograde and atrophic changes in the absence of any indications of previous inflammation. In 325 appendices studied by Zuckerkandl, 23 per cent. presented more or less obliteration of the lumen. A. O. J. Kelly¹ has found a similar state of things in about 25 per cent. of cases. The appendix thus seems to be gradually disappearing, and on general principles might be expected to become readily diseased.

Situated as it is at the head of the cecum, and separated from the cecal cavity by a more or less inconstant fold of mucosa, the valve of Gerlach, it is liable to become the resting-place for foreign bodies or inflammatory exudates which, owing to its dependent position and narrow lumen, are almost certain to be retained within it. Moreover, a slight inflammation of the mucosa about the point of exit of the appendix may even serve to obstruct the discharge of any retained contents.

¹ *Phila. Med. Jour.*, vol. iv., 1899.

Formerly much stress was laid upon vascular disturbances as an important factor in the causation of appendicitis, but there is reason to think that these have been overestimated.

While it is certainly conceivable that embolism or thrombosis of the vessels might occur, and thus produce a necrosis of the structure, this must be a very rare event. It has been proved by Breuer that the artery of the appendix is not an end-artery, but that there are fairly effective anastomoses in all the coats of the organ. Further, the endarteritis and peri-arteritis considered by some to be the chief cause in bringing about necrosis have not been found constantly or indeed even frequently present. In any case they are much more likely to be the expressions of the progressive involution of the structure or else secondary to previous inflammatory disturbance. Still, it must be admitted that kinks or curvatures of the appendix, by hampering the return flow of the blood, not infrequently are at fault in lowering the vitality of the tissue and rendering it a prey to invading micro-organisms.

Another point of importance is the fact that the appendix is particularly rich in lymphoid tissue, much more so in proportion than the large intestine. The lymphoid tissue is found situated diffusely in the mucosa or aggregated into follicles, as in the submucosa. Ribbert and Kelynaek have pointed out that this lymphoid tissue is most marked in childhood, and according to Ribbert it atrophies after the thirtieth year, or in exceptional cases as early as the twentieth. This fact is suggestive when we remember that the majority of cases of appendicitis occur between the ages of twenty and thirty, and even earlier.

The presence of foreign bodies or fecal concretions has always been regarded as a fertile source of appendicular disease, but we think their presence has been somewhat misinterpreted.

Foreign bodies do not invariably cause appendicitis; apple-pips, grape seeds, hair, bits of bone, are not infrequently found in apparently healthy appendices. In the Museum of McGill University is an appendix containing a large number of lead shot, the owner of which never suffered from appendicitis. On the other hand, sharp bodies, such as glass or pins, have been known to provoke trouble.

Fecal concretions are, however, of more real importance. These concretions consist of fecal substances inspissated in a mucoid matrix and often impregnated with lime salts; desquamated epithelium and pus-cells may also be present. While they have been found in normal appendices and have been apparently innocuous, it cannot be denied that they are more frequent in the diseased appendix, especially in the ulcerative and gangrenous type.

In 89 cases of appendicitis analyzed by E. A. Archibald,¹ at the Royal Victoria Hospital, in 38 nonperforative cases concretions were found in 3, while in 41 perforated cases concretions were found in 22. It has generally been forgotten that fecal concretions are an expression of a previous or co-existing inflammatory process rather than the cause of inflammation. Just as in the case of the production of gall-stones, there must have been a pre-existing catarrh of the lumen to produce an excess of mucus, and a desquamation and exudation of cells to form a nidus in which the concretion could form. Once formed, of course, the presence of a foreign body would tend to perpetuate and accentuate the condition. As a rule, however, it is only

¹ *Montreal Med. Jour.*, Feb., 1900.

the larger concretions which, by obstructing the free outflow of the contained secretions, or by pressure upon the mucosa, lead to acute diffuse inflammation or local necrosis and perforation.

The direct exciting cause of appendicitis is the activity of micro-organisms, of which *B. coli*, *Staphylococcus pyogenes albus* and *aureus*, *Streptococcus pyogenes*, and *B. pyocyaneus* are the most important. In Kelly's 400 cases the *B. coli* was present in 92 per cent. ; Tavel and Lanz, Barbacci, and Welch have pointed out the frequency of "mixed" infections. The reason that these are not discovered more often is explained by the fact that *B. coli* readily overgrows and destroys less vigorous germs, and unless plate-cultures are made at the time of operation the weaker germs are not isolated and discovered. It is also likely that even during life the same destruction of the weaker organisms by *B. coli* occurs, so that an appendicitis originally brought about by several germs, when the cultures are made may appear to be due to only one. It should also be stated that microscopic sections of the appendix, appropriately stained to show bacteria, often reveal the presence of germs within the lumen in cases where cultures have failed to develop.

When mixed infection is recognized it is usually *B. coli* and staphylococci. In a few cases the staphylococci or *B. pyocyaneus* have been found alone.

It is difficult to give an accurate classification of the forms of appendicitis, since the manifestations are numerous both in form and degree ; but the following, based on pathologic principles entirely, is suggested :

ACUTE . . .	{	Catarrhal.
		Diffuse or phlegmonous.
	{	Necrosing . . . { Perforative.
		Nonperforative.
	Gangrenous.	
CHRONIC . .	Specific (<i>e. g.</i> , typhoid).	
	{	Catarrhal.
		Obliterating . . . { Progressive.
	{	Relapsing.
		Tuberculosis.
	Specific { Actinomycosis.	

In the **acute catarrhal** form the appendix is swollen, the external venules distended, and the tube is often kinked or twisted. The mucosa is swollen, succulent, with possibly minute hemorrhages, and there may be slight superficial erosion. The lumen contains thin mucus with perhaps a few leukocytes, or there may be concretions ; sometimes adhesions are found about the appendix.

Microscopically the mucosa is swollen, hyperemic, and in a state of acute catarrh. The lymphoid follicles also are prominent and the submucosa seems edematous. The **acute diffuse** form is more severe. All the coats of the appendix are swollen and there may be flakes of fibrinous lymph externally. All the characters of the first form may be present, but the essential point is a diffuse leukocytic infiltration invading all the coats, which are markedly edematous and thickened as a consequence. The lymphoid elements are also proliferated. There may be slight necrosis also of the mucosa, and the cavity may contain mucopus. The meso-appendix is often inflamed.

In the **acute necrosing** type, at some point or other, there is a local

area of necrosis, often corresponding to a fecal concretion, which may be of varying depth or even may penetrate.

The **gangrenous** is an extreme and fulminating form in which the whole appendix is converted into a blackish, sloughy mass.

Typhoid ulceration of the appendix resembles typhoid ulceration elsewhere. Cases of typhoid have been operated on for appendicitis through errors in diagnosis.

Chronic appendicitis may supervene upon an acute attack, or may be chronic, or at least subacute, from the first.

The different forms are characterized by the proliferation of the connective tissues by which the mucous membrane is entirely replaced, or all the coats become fibroid. In some the process is chronic and diffuse in extension, but in others is associated with local round-cell infiltration pointing to acute exacerbations of the trouble.

In long-standing cases the lumen of the appendix is obliterated and the

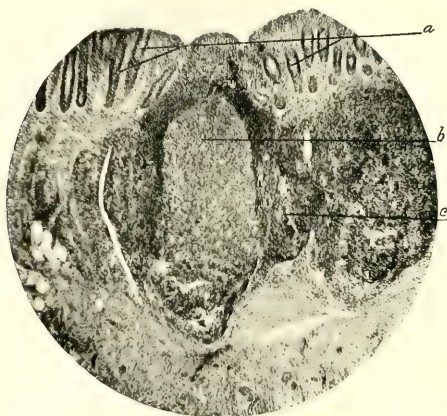


FIG. 249.—Acute catarrhal appendicitis: a, catarrhal crypts; b, hyperplastic lymph-follicle; c, diffuse infiltration of submucosa (Leitz objective, No. 3).

structure is converted into a fibrous cord. If this obliterating process is confined to the proximal portion, the rest of the appendix may be dilated from the production of secretion and a cyst-like structure produced. By obliteration spontaneous cure may thus occur. When perforation or gangrene occurs the result as to death depends largely upon whether local adhesions take place or not. When the appendix is behind the cecum and situated entirely outside of the peritoneal cavity, retroperitoneal abscess may be the result. In other cases, if adhesions form, a local abscess is the result, when there is an accumulation of fetid pus, and in the cavity of which may be found the whole or part of the appendix lying free, or one or more concretions. When no adhesions form general peritonitis and death ensue rapidly.

Local abscesses may burst into the bowel, causing fecal fistula, or may

burst externally. Thrombosis of the veins of the mesentery and great omentum and suppurative portal pylephlebitis are common.

Special Forms of Inflammation of the Intestines.—Typhoid.

—In typhoid the portals of infection are usually the intestine, though exceptional instances have been recently recorded (Roux, Sicard, Dufaud) where the infection was through the lungs.

The characteristic lesions of typhoid are found in the intestines, especially the lower three feet of the ileum and the first portion of the colon. In a few cases the lesions are confined to the colon, as in a case recorded by Hodenpyl.¹ It should not be forgotten that cases of typhoid may occur in which the characteristic intestinal lesions are entirely wanting. Many of the cases possess the characters of a typhoid septicemia. About 25 cases are now on record, confirmed by bacteriologic examination, and the number will no doubt be steadily added to, owing to the perfection of bacteriologic methods and the employment of the Widal test. Cases have been recorded in America by Flexner and Harris,² Nicholls and Keenan,³ McPhedran,⁴ Lartigan,⁵ Opil and Bassett.⁶

In typical cases of typhoid the mucosa is swollen and hyperemic, showing all the signs of acute catarrhal inflammation, but the characteristic changes are seen in the Peyer's patches and solitary follicles. Owing to the invasion of the lymphoid areas by the typhoid bacilli, the patches become inflamed, edematous, and proliferate actively. Thus, the lymphoid follicles become swollen and project above the general surface as flattened plaques which are soft and intensely reddened. In other cases the solitary follicles may be so much swollen that they project as little polyps with a narrow pedicle.

At this period the areas microscopically show a catarrhal mucosa, with intense congestion of the vessels of the same and submucosa. The follicles show hyperplasia, and there is a perifollicular aggregation of lymphoid cells with leukocytes. Leukocytes may even be seen in the muscular coat and as deep down as the serosa. At the height of this first stage the surface of the swollen plaques presents a reticulated or grooved appearance, recalling the convolutions of the brain—plaques à surface réticulée. This appearance is due to the irregular swelling of the lymphoid elements and the connective-tissue stroma.

The exact nature of the process has been the subject of some discussion. Virchow originally thought that the swelling of the plaques was due to edema and inflammatory exudation. This view was subsequently modified by the researches of Rokitsansky and Hoffman. Klein attained something very near the truth; but by far the most thorough and convincing investigation is that of F. B. Mallory,⁷ which has thrown an entirely new light upon the subject.

According to Mallory, the essential lesion of typhoid fever is a proliferation of endothelial cells throughout the body, which he claims is brought about by the action of a diffusible toxin derived from the bacilli. This change is seen in the Peyer's patches, mesenteric glands, liver, and bone-marrow, as well as in the lymphatics and blood-capillaries. The endothelial plates attached to the fibrous meshwork in the lymphoid follicles and mesenteric glands, as well as those lining the various capillaries, proliferate,

¹ *British Med. Jour.*, Dec. 25, 1897.

² *Bull. Johns Hopkins Hosp.*, Dec., 1897.

³ *Montreal Med. Jour.*, Jan., 1898.

⁴ *Phila. Monthly Med. Jour.*, Oct., 1899.

⁵ *Bull. Johns Hopkins Hosp.*, April, 1899; *New York Med. Jour.*, July 29, 1899.

⁶ *Phila. Med. Jour.*, Jan. 19, 1901.

⁷ *Jour. of Exper. Med.*, iii., 611, 1898.

becoming fused into giant cells, and act as phagocytes. These ingest the bacteria and slowly eat up the lymphoid cells, which thus gradually disappear. A few leukocytes can be seen in the follicles and within the crypts of Lieberkühn, but are not at all a prominent feature. The areas of necrosis are produced by obstruction to the circulation, owing to a massing of the endothelial cells within the capillaries and the consequent anemia.

The changes are more marked the nearer to the point of entrance of the infectious agent, but may be demonstrated in the remote parts of the body. In the case of the capillaries the proliferation is most evident in parts where the circulation is slowest. Mallory explains the focal necroses in the liver and spleen, as well as elsewhere, upon this basis.

At the beginning of the second week, owing to the anemia and the toxic action of the bacteria, certain portions of the plaques undergo a form of coagulation necrosis, so that shallow ulcers are produced. The central portions may slough away or multiple shallow erosions may be produced, having a ragged appearance. The eroded portions often have a brownish color from bile staining. According to Marchand, a croupous exudate can be seen upon the surface of the swollen plaques, somewhat firmly attached to the subjacent tissue. In the course of a few days more extensive portions slough away, leaving a fairly smooth base, but the edges of the ulcer are still swollen and infiltrated.

The ulceration usually extends down to the muscularis mucosæ, which forms the base of the ulcer and is recognized by its clean, ribbed appearance. In the well-developed and advanced ulcer the base is smooth and the edges thin and undermined. If the necrotic process extends further, it may reach the serous coat, and not infrequently perforates the wall, leading usually to a fatal peritonitis. Owing to the peculiar asthenic type of the typhoid infection and the fact that leukocytosis is not usually present, but little exudate is thrown out and adhesions do not readily form.

Another frequent complication is hemorrhage which is brought about by the erosion of some vessel in the ulcerated area.

With regard to the frequency of these two complications, the following figures may be cited: In 408 cases of typhoid treated in the Royal Victoria Hospital from 1894 to 1898 inclusive, there were 18 deaths, or a mortality of 4.4 per cent. Of these, 6 were from perforation and 3 from intestinal hemorrhage. Intestinal hemorrhage, including fatal and nonfatal cases, occurred in 3.39 per cent. of all cases.



FIG. 250.—Ileum; typhoid fever (early stage): Peyer's patches and solitary follicles greatly swollen; superficial ulceration.

As a rule, the most advanced ulcers are found in the region of the ileocecal valve, and they seem to extend gradually up the ileum. In severe cases the last portion of the ileum together with the cecum may be converted into a large gangrenous eschar in which islets of mucosa stand out prominently, the ulcerating process having extended far beyond the limits of the original Peyer's glands.

The process of healing varies naturally with the intensity and development of the condition.

The plaques that are merely hyperplastic become again soft and hyperemic through gradual absorption of the inflammatory products. Frequently there is an escape of the red corpuscles from the vessels, so that hemorrhagic infiltration occurs.

When ulceration has occurred the edges of the necrotic area become less

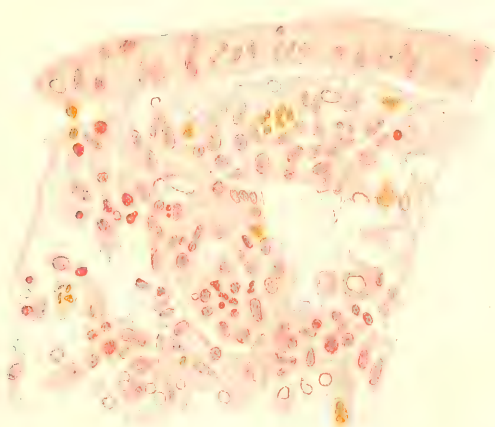


FIG. 251.—Mucous membrane of the intestine, showing diffuse formation of phagocytic cells; also a dilated lacteal filled with phagocytic cells (F. B. Mallory).

tumid and again hyperemic. Not infrequently there is hemorrhagic infiltration of the tissues, which accounts probably for those cases of intestinal hemorrhage which occur late in the disease in the stage of beginning convalescence. The glandular elements of the mucosa through proliferation gradually extend over the base of the ulcer, and thus the original condition is restored.

When the ulcers have been of great extent the glandular regeneration may be incomplete or absent, so that the floor of the ulcer is covered over by a layer of fibrous tissue which may contain no or relatively few imperfect glandular elements.

When the ulcers have healed, their site is often recognized by the fact that there remain oval patches which are smooth, pigmented, and depressed below the general surface of the bowel.

In the first eight or ten days the specific bacilli can be recognized in the Peyer's glands in definite clumps.

Coincidentally with the intestinal affection the mesenteric glands are swollen, hyperplastic, and inflamed; they may be softened, and in occasional instances suppurate.

Tuberculosis.—Tuberculosis is perhaps the most frequent affection of the intestines. As in typhoid fever, the most marked changes are found in the neighborhood of the ileocecal valve, but the distribution of the lesions is apt to be more extensive than in the case of typhoid, for the ulcers may extend from the duodenum to the anus.

In the majority of cases, in adults at least, the process is a secondary one, depending upon the entrance of tubercle bacilli derived from some more or less distant focus into the intestines. Perhaps the most frequent cases are in those suffering from pulmonary tuberculosis who have swallowed their infected sputum. Sometimes also caseous glands may rupture into the esophagus or bowels and thus bring about an infection. A hematogenous infection of the bowel is certainly rarer.

In the case of children, however, intestinal tuberculosis is frequently regarded as a primary infection, owing to their more general use of milk. It is pretty generally acknowledged now that the milk of tuberculous cattle is a source of grave danger to the community. That the milk of tuberculous cattle often contains virulent bacilli which are capable of transmitting the disease to animals fed upon the same has been abundantly proved.

Apart from the specific and characteristic lesion of tuberculosis, certain catarrhal and ulcerative processes, and even diphtheritic and gangrenous inflammations, have been attributed to the action of the tubercle bacillus, but it is still doubtful in how far these may not be due rather to the action of associated micro-organisms.

In the typical manifestation of tuberculosis of the intestines the process begins in the Peyer's patches and solitary follicles as small nodular elevations beneath the mucous membrane. In a short time the center of these becomes of a yellowish-white color, an evidence of central necrosis and caseation. By softening and discharge of the caseous area a small ulcer with infiltrated margins is produced, about which other minute caseous foci appear. These ultimately coalesce, so that a larger ulcer is produced, having the following characteristics: The edges are irregular, infiltrated, but not usually undermined; the base is ragged and necrotic, and frequently in it can be seen small yellowish caseous foci, representing the local metastatic nature of the extending process. The tissues around the ulcer usually show little disturbance, but are sometimes markedly hyperemic, and may even present small hemorrhages.

The process generally extends into the muscular coats, and often to the serous covering, which it does by direct extension along the lymphatics. Thus, a little crop of tubercles forms beneath the serosa, which is coincidentally swollen and infiltrated, surrounded by hyperemic and newly formed capillaries, which are characteristic of the tuberculous nature of the process. Frequently around these can be seen a little knot of dilated channels filled with clear fluid, representing chyle-vessels which at some part of their course have become blocked by the tuberculous infiltration. About these areas there may be slight local peritonitis, evidenced by a slight dulling of the serous surface and possibly a deposit of delicate fibrin.

As the ulcers coalesce and become larger they tend to extend transversely to the long axis of the bowel, forming a girdle-shaped area of erosion. This is explained by the fact that the blood-vessels and lymphatics, along which the tuberculous process extends by preference, run round the bowel.

The condition is usually progressive and terminates in death, but occasionally more or less complete healing takes place. About the margins and bases of the ulcers a firm, scar-like connective-tissue proliferation takes place, which may result in the transformation of the ulcer into a firm cicatrix, and in cases in which a progressive caseation is coincident marked atresia of the bowel-lumen may result.

Tuberculous ulcers do not usually proliferate, but may give rise to fatal peritonitis; more often local adhesions and fistulous communications are produced. *Fistula in ano* has been for years recognized as being frequently due to the perforation of a tuberculous ulceration of the rectum. Fatal hemorrhage is also uncommon, but small oozings of blood are not infrequent.

The mesenteric glands are not infrequently caseous.

Microscopically at the edges and the base of the ulcer can be made out a

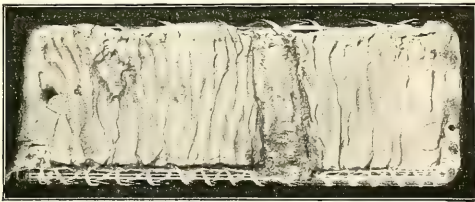


FIG. 252.—Tuberculous ulcers of the ileum.

layer of ordinary granulation-tissue of varying thickness, which, as a rule, shows only a moderate degree of caseation or destruction. In this layer are embedded more or less numerous tubercles, with the usual epithelioid and giant-cells, showing a certain amount of central caseation. In certain cases the tubercles can be found not only at the edge or base of the ulcers, but in the muscular and serous coats as well. By special methods tubercle bacilli can be made out in the tuberculous foci. A further point is the presence of great numbers of "mast-zellen" in the submucosa or muscularis.

The muscular coat shows a certain amount of fatty degeneration.

An interesting form of tuberculosis of the intestine is the productive hyperplastic variety: this affects especially the cecum, and tumor-like masses are produced. Crowder¹ has presented an excellent study of this form.

Syphilis.—Syphilis of the intestines frequently is found in the rectum, just about the anus. The primary sore can under certain circumstances be found there, as well as syphilitic condylomas and papules. More often it takes the form of gumma.

The inflammatory process in the last form is usually situated in the submucosa, and leads to extensive ulceration of tissue. When recent the surface

¹ *Am. Jour. Med. Sci.*, cxix., 668, 1900.

exudes pus. In severe cases, for a distance of 10 or 12 centimeters above the anus the mucosa may show almost complete destruction, there being only a few islets of undermined mucosa left.

As the case progresses reparative fibrous hyperplasia takes place, so that marked stricture of the rectum may take place, with all its attendant disorders of obstruction, hypertrophy, and ulceration. Occasionally gummatous foci develop in the perirectal cellular tissue and lead to external or internal fistulae.

In the colon and small intestines lesions, at least in acquired syphilis, are rare, but ulcers, radiating scars, and nodular infiltrations of the intestinal

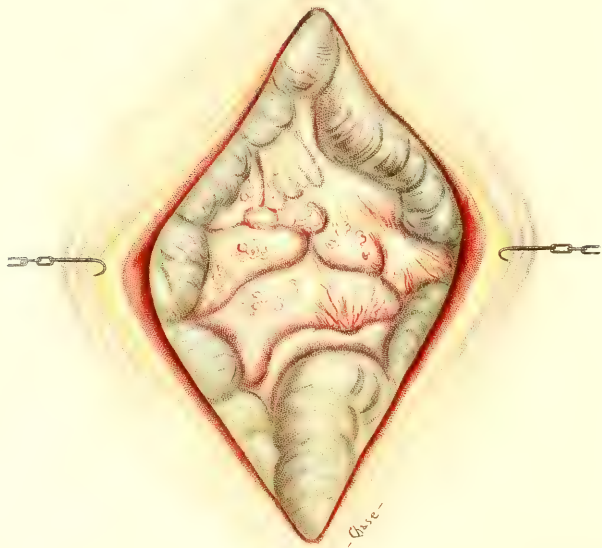


FIG. 253.—Tuberculosis of the mesenteric glands (Riesman).

wall have been described. In hereditary syphilis the small intestine is perhaps most frequently affected, and, in contradistinction to the other infectious lesions, it is the upper portion, usually the jejunum, which is affected.

Cholera.—It is almost impossible postmortem to differentiate the lesions of cholera nostras, cholera Asiatica, and the enteritis found in diabetic coma and acute arsenic poisoning one from the other. In such cases reliance must be placed upon the bacteriologic examination.

In Asiatic cholera during the earlier stages the intestinal mucosa is more

or less reddened, particularly about the solitary and agminated glands. The redness is bright or even of a dull-brown color; the veins are congested; the mucosa as a whole is catarrhal and edematous; and the various lymphoid nodules are unusually prominent, presenting a somewhat granular appearance. In the typhoid stage the swelling has usually disappeared.

The surface of the intestine is usually covered with thick, grayish mucus containing desquamated cells. The intestines contain a considerable quantity of clear, thin fluid, alkaline in reaction and poor in albuminous constituents, with delicate white flakes in it—rice-water stools. Chlorid of sodium and carbonate of ammonium are to be found.

Microscopically there is at most a slight cellular infiltration of the mucosa and submucosa, with sometimes considerable necrosis of the epithelial cells of the gland-crypts.

Koch's comma bacillus can be found in the intestinal contents.

Actinomycosis.—Infection is supposed to arise from the use of contaminated water or vegetables. Leith¹ has discussed the subject at some length. The condition is characterized by the formation of whitish patches in the intestinal mucosa, with proliferation of the submucosa. As the disease progresses ulceration takes place, and external fistulæ are not uncommonly produced, in which the characteristic yellowish grains may be found, as in



FIG. 254.—Carcinoma of the rectum: *a*, mucous membrane; *b*, muscularis mucosæ; *c*, beginning of aberrant growth; *d*, masses of columnar cells with tendency to form lumina. Leitz objective, No. 3.

the case of a boy of eight recorded by Krasnobajew.² The appendix has in several instances been regarded as the most likely starting point, the disease beginning with symptoms of appendicitis; subsequently large retrocecal abscesses containing ray-fungi have been formed or external fistulæ have developed. In many cases of abdominal actinomycosis with external per-

¹ *Edinb. Hosp. Rep.*, ii., 128, 1894.

² *Arch. f. Kinderheilk.*, Bd. xxiii., Hefte 1-3.

forations and intraperitoneal adhesions it is impossible to find the exact starting point of the process.

Tumors.—Carcinoma.—With the exception of the flat-cell carcinoma which begins at the anus and that which starts from Brunner's glands, the carcinomas formed in the bowel are of the cylindric-cell type (Fig. 254). Since they are composed mostly of cells retaining the characteristic gland-type, the majority of these growths belong to the adenocarcinomas. Of the other types may be mentioned the medullary, the colloid, and the scirrhus cancer.

Carcinomas are most frequently found in the large intestine, in the rectum, about the ileocecal valve, the iliac, splenic, and hepatic flexures, and the



FIG. 255.—Adenoma (papillomatous) of the colon with early carcinomatous change.

cecum. In the small intestine the site of election is in the neighborhood of the bile-papilla.

A striking fact is the relative frequency with which intestinal cancers occur in young people; this is probably connected with the frequent presence of mucous polyps in children.

The new growth forms either a solitary, sharply defined fungous mass, or is diffused over a considerable area of the intestine. It seems to have a special tendency, particularly in the rectum, to form a ring-shaped growth. The muscular wall is infiltrated and hardened, so that the intestine is converted into a stiff, uncollapsible tube. Very generally the surface ulcerates, producing a shallow loss of substance with fibrous scarring of the edges and base, and thus a well-marked stricture is the result. The affected bowel

may become adherent to neighboring structures or the cancerous ulcer may perforate, leading to peritonitis.

Metastases in the lymph-glands, peritoneum, and liver are common. Secondary carcinomas are as rare as the primary are frequent. They may occur from implantation of cancers of the pancreas, stomach, uterus, or vagina; or may be metastatic.

Of connective-tissue tumors may be mentioned fibromas, lipomas, myomas, angiomas, and sarcomas; all are comparatively rare.

Of **sarcoma**, round- and spindle-cell forms have been described, as well as alveolar and melanotic growths. The round-cell sarcoma is the commonest, but is still rare; it usually occurs between the ages of forty and fifty. E. A. Robertson¹ has recorded a case in a child of four, where the growth was in the neighborhood of the ileocecal valve.

Lymphosarcoma occurs as a primary or secondary growth. The new growth starts from the lymphoid follicles, but may begin independently of them. Sooner or later the process extends beyond the limits of the follicles and invades the mucosa and other coats of the bowel. In the secondary form the invasion comes from the affected mesenteric glands.

THE LIVER.

The liver is an organ which bears, on the one hand, an important relationship to the alimentary system, excreting as it does a fluid—bile—that assists in the digestive functions; and, on the other hand, to the blood, since it is to be regarded as one of the hematopoietic viscera, and in addition pours into the general circulation nutritive materials derived from its internal metabolic processes. Its functions are to secrete bile, which is derived indirectly from the blood, together with biliary acids the products of the metamorphosis of albuminoid substances, both of these forming the external secretion of the gland; to convert glycogen into sugar and proteids into urea, which substances are poured into the blood and afford an important index of the processes of nutrition and the systemic metabolism. The liver, further, is an important storehouse for fat.

Anatomically the most important point is that the liver possesses a double blood-supply; from the portal vein bringing to it the nutritive substances from the digestive tract, and from the hepatic artery which supplies the blood necessary for the growth and nourishment of the hepatic tissues themselves. Both these vessels unite within the lobule, about midway between the center and the periphery, and pour their united blood into the intralobular vein. The intralobular veins of several adjacent lobules unite to form the sublobular veins, and these later form the branches of the hepatic vein, which empties its blood into the vena cava inferior.

The bile is excreted through the common bile-duct, which empties into the duodenum at the bile papilla.

From these considerations it will be seen that the liver is liable to disorders arising from many sources: Inflammatory processes spreading up the bile-ducts or the portal veins, and obstructions of many kinds, lead to serious pathologic disturbances in the liver itself, which alter metabolism and so react upon the general system; and, conversely, systemic disorders, infective, circulatory, or degenerative, can affect the liver and its functions.

¹ *Montreal Med. Jour.*, Jan., 1898.

Malformations.—Complete **absence of the liver** is rare. Much commoner are variations in shape or in the number of the lobes; the liver may be thin and flat, or again may resemble a short, truncated pyramid. A relatively common condition is for the left lobe to be prolonged backward and downward, forming a definite lingula.

Accessory livers are found occasionally situated in the suspensory ligament. Cases are recorded of absence of the gall-bladder and abnormal dilatation or narrowing of the bile-ducts. The so-called Liebermeister's grooves are common, occurring in 5.6 per cent. of autopsies. They consist of several shallower or deeper grooves on the convexity of the right lobe, directed forward. They do not correspond with the direction of the ribs, and have received different explanations. Liebermeister thought they were due to pressure from difficult expiratory movements, while Zahn attributed them to the action of a hypertrophied diaphragm. It is probable that most cases are congenital.

The liver may be **reversed** and lie on the left side in the condition of transposition of the viscera. It also may be dislocated in diaphragmatic, umbilical, or abdominal hernia.

Of **acquired deformities** the most frequent is the "lacing-lobe." Owing to the pressure of a tight corset the lower portion of the thoracic wall is driven in, so that a transverse fissure is produced, which divides the right lobe into an upper and a lower portion. The capsule at the fissure is thickened and opaque white in color, while the subjacent acini are atrophic. A portion of the liver may be almost separated from the main body, being only connected by a fibrous band, or, indeed, may be separated altogether. The condition is found in short-waisted people. Tight lacing in those with long waists is more likely to produce a movable kidney.

Owing to a laxness of the suspensory ligament, the liver may be tilted forward or lie lower down in the abdomen than usual. This is generally seen in the condition of enteroptosis. A floating liver may thus be produced. Abnormal position may also be produced by pleural exudates, emphysema, tumors of the thorax, and the like.

Circulatory Disturbances.—**Anemia** is either part of a generalized anemic condition or is due to some local disturbance, such as pressure upon the liver or swelling of the parenchyma. Congestive hyperemia is frequently found, as, for instance, after a meal, at the beginning of acute inflammations, or from any cause leading to hyperemia of the gastro-intestinal tract.

Passive congestion is brought about by obstruction to the general circulation or pressure upon the hepatic vein. Among the conditions bringing this about may be mentioned: Stenosis and insufficiency of the mitral or tricuspid valves, heart-weakness, emphysema of the lungs, indurative pneumonia, right-sided pleuritic effusions, the pressure of aneurysms or enlarged glands upon the inferior vena cava.

In the early stages the liver is enlarged, soft, and full of blood; the central veins of the acini are distended, and on section the organ may drip blood. Later on the liver is somewhat diminished in size, the surface uneven and finely granular. On section the appearance is that of a nutmeg; hence the term "nutmeg-liver." This peculiar appearance is due to the fact that the center of the lobule is congested and somewhat depressed below the general surface, while the periphery of the lobule is pale yellow or yellowish brown and swollen, due to the presence of fat in the secreting cells. In

some cases reddish patches are seen, which are regenerated lobules. In the most advanced stages the dark, congested appearance becomes general. The organ becomes firmer, owing to the production of fibrous tissue; this condition is called cyanotic induration.

Microscopically the intralobular veins are distended with blood, together with the capillaries leading into them. In an advanced condition all the capillaries of the lobule are distended. The columns of liver-cells between the capillaries being thus compressed, the secreting cells become atrophic and are filled with yellowish-brown granules of pigment, and show fatty degeneration. The degeneration is most marked in the central and middle zones of the lobule. The condition may be so extreme that numbers of the liver-cells actually disappear, and are represented only by little masses of pigment.

In certain cases in which congestion is gradual in its onset there are induration and fibrous-tissue proliferation, a condition which is generally found about the radicles of the hepatic vein, but is also present in the periportal districts. The portal sheaths in this case show a cellular infiltration. Thus a form of cirrhosis is the result.

Besides the condition of general passive hyperemia just mentioned, a sporadic form has recently been described, principally in livers affected by metastatic growths, in which areas of complete atrophy are sharply separated from comparatively healthy liver-tissue. This is probably due to closure of certain of the venous capillaries.

Allied to passive hyperemia is a form of **hemorrhagic infarction** due to the closure of radicles of the portal vein through thrombosis or embolism. In this the liver structure remains, owing to its receiving nourishment through the hepatic artery. In cases in which the central capillaries in the lobules are affected, which are formed by the union of the capillaries of the hepatic artery and the portal vein, atrophy and even necrosis of the liver-tissue may result. Schmorl and Prutz have described this condition in connection with eclampsia. Embolism of the hepatic artery or its branches, particularly if assisted by heart-weakness, leads to the formation of an infarct (Chiari).

Minute **hemorrhages** into the liver substance, and seen frequently beneath the capsule, occur from traumatism, the hemorrhagic diathesis, and various infections.

In leukemia the capillaries are everywhere distended with leukocytes, and specially prominent collections can be seen in the portal districts (Fig. 256).

Edema of the liver is found occasionally, and leads to enlargement, whereby the liver substance is more succulent than normal, with a pale, dull, shining appearance on section. Birch-Hirschfeld has attributed icterus neonatorum to compression of the bile-ducts by edematous connective tissue.

Retrogressive Changes.—**Simple atrophy**, in which there is a uniform diminution in size of the secreting cells, is found in marasmus, old age, and the various cachexias. The form due to pressure has already been referred to. Cancerous disease of the esophagus and stomach has a special tendency to cause atrophy of the liver. The atrophy affects chiefly the anterior border of the liver, which becomes sharper, and may eventually be composed of supporting structure merely, every vestige of liver-cells having disappeared. The rest of the parenchyma is harder than normal in conse-

quence of a relative increase in the connective tissue, and is often deeply pigmented (brown atrophy).

Frerichs has called attention to a form of atrophy—melanemic atrophy—apparently caused by blocking of the capillaries with black pigment.

In acute yellow atrophy of the liver there is rapid diminution in size. This disease is considered further on page 806.

Cloudy swelling is a frequent condition in the acute infective fevers, particularly typhoid fever and scarlatina; it may also be due to the action of bacterial toxins, apart from elevation of temperature. Cloudy swelling is hardly distinguishable from acute parenchymatous hepatitis (page 805). A liver affected in this way on section seems slightly succulent, and the lobules are no longer readily distinguishable, giving the cut surface a peculiar glassy, fused appearance. It is surprising how little change can be recog-



FIG. 256.—Liver—leukemia: *a*, liver-cells; *b*, capillary distended with leukocytes. Leitz objective. No. 7.

nized microscopically; at most, the cells are a little swollen and lose their polygonal character, while the nucleus is a little obscured.

Fatty changes often follow upon a pre-existing cloudy swelling, but may occur in the course of severe anemias, particularly pernicious anemia, and from the action of various poisons, notably phosphorus. In advanced cases of so-called *fatty degeneration* the liver is somewhat diminished in size, its capsule is wrinkled, and it feels doughy on pressure; the color is bright yellowish or yellowish brown. On section it is very soft and friable, and fat-droplets can be scraped off the cut surface with the knife.

Microscopically the liver-cells, particularly those of the peripheral portion of the lobule, are seen to contain small clear droplets which represent the fatty substance. In an advanced condition it may be hard to recognize any liver structure at all except the portal sheaths. A certain amount of fatty change is seen in cases of passive congestion and in the neighborhood of septic foci or new growths.

The liver serves normally as a storehouse for fat, and consequently a certain amount of fat can be recognized in almost every liver-section; thus, after a meal the liver contains a noticeable quantity. Any cause, however, which interferes with the proper oxidation of fat or which results in too great a supply of fat to the organ may lead to *fatty infiltration*. In this condition the liver is somewhat enlarged, though its specific gravity is lessened; the edges are rounded; the surface is yellowish brown or bright yellow according to the amount of fat present; and the surface can be readily indented. On section it is friable, and oily globules can be scraped off. If very fatty, small portions may actually float in water.

Microscopically the appearance is much the same as in fatty degeneration, and in advanced cases neither form can be distinguished from the other. In so-called fatty degeneration the tendency is at first for small droplets to be formed, which ultimately coalesce. In cases in which the periphery of the lobule is fatty and the center relatively free the condition of fatty nutmeg-liver is the result.

Amyloid degeneration of the liver, like that of other organs, is found in chronic diseases, especially in those associated with suppuration or continuous excretion; for instance, tuberculosis of the lungs, chronic pyemia, bone disease, syphilis, and chronic malaria. The liver is enlarged, its edges rounded, and its consistence increased, giving the organ a somewhat leathery feel. When placed flat on a table the edges do not touch the surface, as they would do in the case of a normal liver. On section the cut surface looks as though it were spread with a layer of gelatin, and the edges are translucent. The amyloid masses can be recognized by their transparent, jelly-like appearance. The intervening liver substance will vary in appearance according to the amount of fat present and the degree of congestion.

When a watery solution of iodine is poured over the cut surface the amyloid portion takes on a rich mahogany-brown color. The gall-bladder usually contains thin, clear bile.

Microscopically the amyloid substance is seen to occupy by preference the middle zone of the lobules, leaving the center and periphery free. The material is probably rather of the nature of a deposit, which is laid down in the walls of the capillaries, in the form of glistening scales, between the endothelium of the capillaries and the liver-cells. In advanced cases the larger arterioles of the portal sheath are affected, the middle coats especially showing the change. The secreting cells which lie between the affected capillaries, owing to the pressure, show various grades of fatty change and atrophy.

Focal Necrosis.—In certain infective fevers, particularly typhoid fever, variola, cholera, etc., and in various intoxications, small local areas of necrosis—focal necroses—are seen, which are visible to the naked eye as grayish or dirty-yellow dots the size of a pin-head or less. These are small areas of necrosis of the liver-cells, or perivascular collections of small round cells resembling lymph-follicles.

Pigmentation.—Normally in the liver-cells, when we examine sections with a high power, we see a considerable amount of a golden-yellow pigment in the form of fine granules. For reasons already stated, there is some ground for concluding that these are not inspissated bile, as is usually taught, but are really the bodies of bacteria in a dead or dying condition which have become bile-stained; under pathologic conditions, however, the pigment of the liver is much increased.

In *icterus* the liver alone or together with all the organs of the body may be stained a bright yellow. This condition is due to a more or less extreme obstruction of the larger bile-passages, or even of the fine bile-capillaries. Hunter is inclined to think that all forms of hemohepatogenous jaundice are due to obstruction, and that in cases in which no gross evidence of obstruction exists there is a catarrh of the finer bile-capillaries.

Among the frankly obstructive causes may be mentioned cholelithiasis, cholangitis, cancer or other tumors pressing upon the bile-ducts.

Icterus also occurs in various forms of cirrhosis, acute yellow atrophy, and in severe blood destruction. Other types of pigmentation are seen in brown atrophy and in hemosiderosis.

In a moderate grade of icterus the finer bile-ducts on section are distended and bile flows readily from them, while the central portion of the lobules shows a diffuse bile staining. Microscopically the liver-cells are

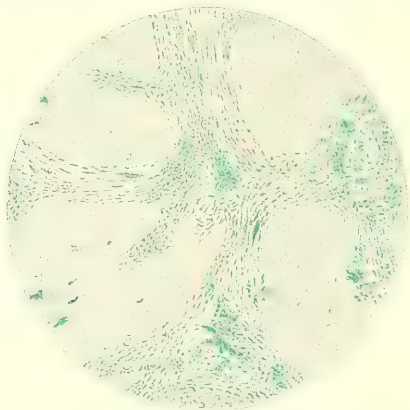


FIG. 257.—Hemochromatosis and cirrhosis of the liver. Iron reaction with potassium ferrocyanid and hydrochloric acid. $\times 100$.

stained a diffuse bright-yellow color or are filled with yellowish or yellowish-brown granules, more rarely with a crystalline pigment (bilirubin). According to Nauwerck and Fütterer distention of fine intracellular passages is produced.

In more severe forms of icterus the liver is diffusely colored and may present a greenish or olive tint.

In advanced conditions of passive congestion, particularly where induration is beginning, an excess of brownish pigment can usually be seen in the secreting cells.

Hemosiderosis is a condition in which, owing to extensive destruction of the red corpuscles of the blood, such as occurs in pernicious anemia, hemoglobinemia, severe burns, and in some cases of cirrhosis of the liver and pancreas, an iron-containing pigment is deposited in the cells, principally at the periphery of the lobules, but also extracellularly in the portal sheaths. The pigment (hemosiderin) is of a golden color, but may be

differentiated from bilirubin by the fact that when treated with hydrochloric acid and potassium ferrocyanid it gives the Prussian-blue reaction (Perl's test). Some iron-free pigment is usually also present. While a minute quantity of iron is present in normal livers, this amount may be increased tenfold in pernicious anemia, as Quincke has shown.

Of other pigments may be mentioned those consisting of foreign substances, either inhaled or taken into the alimentary system, as in the conditions of anthracosis and argyria. Welch has reported a case of anthracotic cirrhosis.

Progressive Changes.—The liver is one of the organs that exhibit in a striking degree the power of repair, not only of its specific secreting elements, but also of the connective tissue, bile-ducts, and blood-vessels. These regenerative powers are seen both in the case of traumatism and in the various degenerative processes, such as are met with in passive congestion, acute yellow atrophy, infective fevers, and in cirrhosis. According to Ponfick and von Meister, from a half to three-fourths of the liver can be removed, and while the original lobes are not reproduced, the remaining liver substance undergoes compensatory hypertrophy. How this is brought about is a matter of considerable doubt. Podwyssozki believes that the new liver-cells are formed from the old ones and also from bile-capillaries. It is clear that certain of the parenchymatous cells are much larger than others, and contain large nuclei which are rich in chromatin and often show evidences of mitosis. The nature of these proliferating cells is not so clear. In this connection should be mentioned the theory recently enunciated by Adami, that in many organs there are present cells which are normally latent, and form a germinating or cambium layer—mother-cells—which under appropriate stimuli proliferate and form daughter-cells, and it is these daughter-cells which have the power of restoring lost tissues, and indeed may produce actual tumors.

Not every enlargement of the liver is to be regarded as hypertrophy, since increase in size occurs in a variety of infiltrations and degenerative processes. Hypertrophy is a homologous increase of the tissue-cells without pre-existing destruction of the same. The existence of a true general hypertrophy is doubtful. Partial hypertrophy can undoubtedly occur. It is seen well in atrophic cirrhosis, the nodular projections of which are to be regarded rather as local hypertrophies—adenomas—than as produced solely by the contraction of the newly formed connective tissue, according to the usual explanation.

Inflammations.—From histologic considerations we can divide inflammations of the liver into the acute parenchymatous, the acute exudative interstitial, and the chronic productive interstitial hepatitis. It must be said, however, that these forms are not sharply defined one from the other, but that various combined or mixed forms occur.

The **acute parenchymatous hepatitis**, a form which is largely degenerative in origin and hardly distinguishable from cloudy swelling, is a fairly frequent event in the course of the infective fevers, particularly typhoid, tuberculosis, pneumonia, and septicemia. The liver is slightly enlarged, and on section is pale grayish and friable. Microscopically the specific cells are swollen and granular, whereby the nuclei are slightly obscured. Not infrequently there is to be seen in the periportal connective tissue small aggregations of leukocytes, which may even penetrate between the liver-cells them-

selves. Where restoration to the normal condition is beginning the affected cells become fatty, hyaline, and often vacuolated. While certain of them disappear, others appear to proliferate, so that there is an actual increase in the number of the nuclei. The condition seems to be a combination of a degenerative process together with a reactive and reparative inflammation.

Allied to this condition are those rarer cases in which degeneration and atrophy are the marked features, the regenerative process being rather in the background, a condition in which clinically the shrinkage of the liver can be followed from day to day, and which is properly termed acute atrophy of the liver. Of this type is the **acute yellow atrophy**. This disease, which is generally fatal, begins acutely with signs of a severe systemic intoxication—high fever, delirium, convulsions, coma, multiple hemorrhages, and a quickly



FIG. 258.—Acute yellow atrophy of the liver: *a*, areas of necrosis of the liver-parenchyma; *b*, round-cell infiltration; *c*, regenerated bile-capillaries. Leitz objective, No. 8.

developing jaundice. In the early stages the liver is usually enlarged, but very quickly diminishes in size.

The liver may be reduced to one-half its original size, the capsule is wrinkled, and the consistence rather tough. On section the vessels contain thin blood and the bile-capillaries thin bile; the parenchyma is of a bright lemon-yellow color, with numerous patches of a dark brownish red; usually the reddish color predominates in the left lobe. The yellow patches are soft and somewhat projecting, while the red are denser, firmer, and more of a leathery consistency. Small hemorrhages are numerous in the substance.

Microscopically the yellow patches show extensive fatty changes of the parenchymatous cells, bile-pigment, and bilirubin-crystals. The red areas show only isolated liver-cells or their remains, and are composed mainly of a network of capillaries, in the meshes of which lie a detritus of broken-down cells, blood, and pigment. The condition has a great resemblance to that of phosphorus poisoning, but differs in this respect, that the fatty degen-

eration begins in the center of the lobule, while in phosphorus poisoning it is at the periphery.

The **acute exudative inflammation** may be simple, but is most frequently suppurative, and depends on the action of micro-organisms which gain entrance either through the general blood-stream, from the portal vein, or from the bile-passages. In rare cases a retrogradé metastasis from the superior vena cava may be a cause. Infection from the umbilical vein in newborn children is an occasional occurrence.

The etiology of the so-called **tropical abscess** is by no means yet thoroughly understood; no doubt, many cases are due to a metastatic infection from various forms of dysentery, but there are others in which the cause is by no means obvious, and various dietetic errors, abuse of alcohol, and unaccustomed methods of living, have been considered to be of etiologic importance. Some of the cases may represent the first manifestations of a generalized infection.

Perhaps the most frequent causes of infection from the systemic circulation are ulcerative endocarditis and infected wounds. The causes acting through the portal vein are most commonly appendicitis and perityphlitis, or affections of the intestine, stomach, spleen, and pancreas. In mild grades one sees possibly some soft septic clot in the branches of the portal vein, and on the surface of the liver large irregular areas of a pale-yellow color penetrating somewhat into the liver substance; these are local areas of necrosis and disintegration.

In the severer or more long-standing cases a septic thrombophlebitis is the result, with the production of a periportal suppurative inflammation; the center of the inflammatory areas breaks down and liquefies, thus forming abscesses. Such abscesses can be single or multiple and form rounded suppurating foci about the radicles of the portal vein, which may coalesce, thus forming larger collections. The rest of the liver is congested and more or less swollen and cloudy.

The cases are usually fatal, but some instances occur in which the abscesses rupture into the lung or into the intestine. Healing may take place, with absorption or evacuation of the pus and the production of a fibrous scar.

A specific form of liver-abscess due to *Amœba coli* should be mentioned. The amebæ gain entrance apparently through the portal circulation; often three or four large abscesses are found, which are filled with somewhat characteristic pus of the color of anchovy sauce, in which the amebæ can often be recognized.

Another type of acute inflammation is that due to irritants reaching the liver by way of the bile-passages. Obstruction to the outflow of bile, either in the larger ducts or within the liver itself, may lead to a small round-cell infiltration in the portal sheaths, which may, like the last form, develop into a suppurative inflammation. A cholangitis is thus a frequent cause. The most common germ found in such conditions is the *B. coli*, but both *pus-cocci* and the *B. typhi* have been frequently found.

Under the term **chronic interstitial** or **productive hepatitis** are included a variety of conditions, which, while differing in respect to their etiology and the finer morbid changes, have this in common, that there is an overproduction of fibrous tissue, leading to marked interference with the functions of the organ.

Much confusion has arisen in the discussion of the various forms, largely

owing to a lax use of terms. Many classifications have been proposed, but the one suggested here, based entirely upon pathologic grounds, seems to us to include all forms, and would also seem to be a natural one for reasons given at the beginning of this section. We can recognize, then, the following types of fibrosis or cirrhosis of the liver :

- | | | |
|----------------|---|--|
| INFLAMMATORY : | { | I. Portal cirrhosis with enlargement. |
| | | II. Portal cirrhosis with atrophy (Laennec's cirrhosis, hobnailed liver, gin-drinkers' liver). |
| | | III. True hypertrophic biliary cirrhosis (Hanot). |
| | | IV. Obstructive biliary cirrhosis with enlargement. |
| | | V. Obstructive biliary cirrhosis with atrophy. |
| | | VI. Cirrhosis from perihepatitis. |
| | | VII. Pericellular or diffuse cirrhosis. |
| DEGENERATIVE : | { | VIII. Arteriosclerotic and senile. |
| | | IX. Intralobular (cyanotic induration). |

The first form here mentioned is, in our opinion, but the early stage of Laennec's cirrhosis, for we have met with more than one case in which the liver was at first undoubtedly enlarged, and at death many months later the ordinary hobnailed liver was discovered. That this early enlargement is due to hypertrophy, however, must be doubted; all enlargement is not hypertrophy, and it is unfortunate that the term "hypertrophic" should have been used in connection with cirrhosis at all. In this case the enlargement is far more likely to be due to acute congestion and inflammatory infiltration. Hypertrophy undoubtedly does occur in cirrhosis, but it is a reparative process, and probably only occurs somewhat late in the course of the disease, and it always falls short of the amount necessary to restore the perfect function of the organ.

Atrophic Portal Cirrhosis (*Laennec's*).—In this form the liver is more or less diminished in size—in fact, may only be half the normal weight. The surface is granular with fine or coarse nodules, ranging in size from that of a pin-head to that of a bean. The projections have mostly a bright-yellow or yellowish-green color, whence the term cirrhosis; the color is due to the presence of fat and bile-pigment. The granulation is often most marked in the left lobe and on the anterior border. The nodules are supposed by many to be due to the pressing outward of the liver-tissue by the contracting fibrous bands; but another explanation has been given, that they are composed of masses of hypertrophied liver-cells, a condition akin to adenoma. Indeed, it is most probable that in advanced cases no vestiges of the original liver-cells remain.

On section the organ cuts firmly, and it is seen that the depressions on the surface are associated with bands of fibrous tissue which form a network throughout the liver, in which the liver substance is seen in the form of sharply defined islets. The fibrous bands are of a whitish or reddish-gray color, slightly translucent in appearance, and project above the general level, so that the cut surface is also granular.

Microscopically the connective-tissue proliferation is still better made out. The newly formed fibrous tissue is laid down most abundantly in the periportal regions, and while in advanced cases it may insinuate itself between the liver-cells, so that an intra-acinous fibrosis results, this is never a

striking feature in the picture. When the process is active the portal sheaths are seen to be densely infiltrated with small round cells, which are in part fibroblasts, but probably also leukocytes. In the older portions of the tissue, or where the process has about run its course, the round cells are few, and we see instead dense bands of fibrous tissue of the characteristic fibrillated texture with elongated nuclei.

In these newly formed fibrous bands are found the newly formed bile-capillaries, so called. There is even yet much doubt as to their origin. They are generally more abundant in the areas of cellular infiltration, for as the scar-tissue is produced it seems to crush many of them out of existence. The bile-capillaries may be fairly abundant, but cases are seen in which the proliferation of the bile-capillaries is only slight or may be absent altogether. In any case, their number is never so pronounced in atrophic cirrhosis as it is in the obstructive type of biliary cirrhosis. Some of the ducts are seen to be actual overgrowths from the older bile-passages, others again are grouped into rounded clumps which recall the normal arrangement of the liver-lobules, while still others lead into the liver-lobules by direct continuity of cells.

Thus three modes of development seem possible—proliferation of the original bile-capillaries, persistence of the intralobular bile-capillaries after the liver-cells have disappeared, and finally “reversionary degeneration” of the liver-cells. On careful examination one sees that many of these so-called capillaries do not resemble real capillaries so much as they do atrophied liver-cells, for the protoplasm of the cells stains strongly with eosin, so as to resemble closely the tint of the perfect liver-cell, thus suggesting their origin. Such pseudocapillaries probably represent, then, the original columns of liver-cells within the lobules which have reverted to a more primitive condition.

In addition, blood-vessels are seen in the fibrous bands, which are not only numerous, but wide and thin-walled; these can be injected through the trunk of the hepatic artery. On the other hand, the branches of the portal vein, either from external pressure or from changes in the intima, are more or less occluded, so that the portal circulation sooner or later becomes greatly interfered with. As a result anastomoses are opened up between the gastric, hemorrhoidal, lumbar, spermatic, and esophageal veins. When compensation fails ascites supervenes.

The liver-cells themselves often show little change, but at the margins of the fibrous bands are often atrophic, being reduced to flattened scales or even little more than nuclei. Some show fatty changes. This atrophy is to some extent due, no doubt, to pressure of the contracting bands, but interference with the blood-supply and the influence of circulating toxins also play a part. Occasionally there is marked fatty infiltration, so that we can recognize the fatty cirrhotic liver. Besides this there is some evidence of an attempt at repair, for here and there lobules are met with which are composed of very large liver-cells which stain deeply, as young cells generally do, and may show nuclear proliferation.

Pigmentation is a frequent condition in which granules of a yellowish-brown or yellowish-green color are seen within the liver-cells in the periportal connective tissue and in the endothelial cells of the vessels. This is generally regarded as bile-pigment, but in certain cases the granules are composed largely of iron, and cases are on record in which such large

quantities of this iron-pigment were produced that most of the tissues of the body, including the skin, were of a blue-gray color; this is the condition known as hemachromatosis (Fig. 259). Such cases seem to be associated with marked destruction of the red corpuscles of the blood. The most recent views upon the nature of the pigment of the liver and the condition of hemachromatosis have already been touched upon.

Hanot's Cirrhosis.—In this form, which is rare in this country, the liver is much enlarged, weighing from 2 to 4 kilograms. The surface is smooth, or at most covered with flat prominences which seem to be connected with vascular disturbances. On section the liver is firm and grates under the knife. The cut surface is yellowish or yellowish-green from bile staining, and presents a fine granulation giving the appearance of shagreen leather. This form is associated clinically with jaundice and enlarged spleen, and runs its course with enlargement, giving place to atrophy.

Microscopically the changes are largely degeneration in the parenchyma-

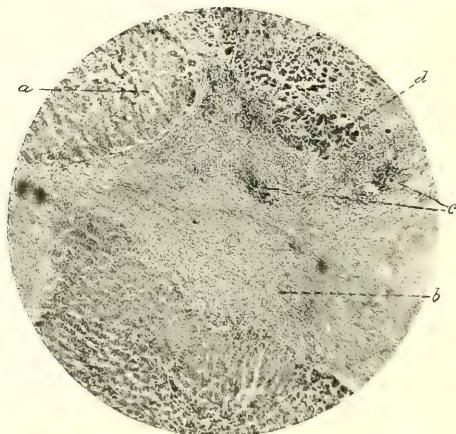


FIG. 259.—Liver—atrophic cirrhosis and hemachromatosis: *a*, liver-lobule; *b*, broad fibrous band; *c*, iron-pigment (extracellular); *d*, iron-pigment (intracellular). Leitz objective, No. 3.

tous cells, which are replaced by a fairly diffuse or pericellular deposit of fibrous tissue of a singularly transparent nature, containing few fibroblasts. The islets of liver-cells remaining are small, and single cells or groups of two or three are often seen isolated from the rest by delicate strands of fibrous tissue. In this form there is also considerable production of bile-capillaries; bile staining is also a marked feature.

Obstructive Biliary Cirrhosis.—This form is dependent largely upon some obstruction to the free outflow of bile either from within the duct, as from a stone, carcinoma, or a fibrous stricture; or from without, as in the case of a carcinoma of the head of the pancreas or of the lymph-glands about the hilus. Obstruction alone does not seem to be the cause, at least in man, for cases occur of cancer of the duct with complete obstruction without the production of cirrhosis; apparently another factor is necessary,

that of inflammation, which is readily produced by the germs which are invariably to be found in the bile-passages in such cases, since a catarrh is always present, a catarrh which is indeed the original cause of the formation of the gall-stones. In one form the liver is much enlarged; in one of our cases, in which a stone was present in the hepatic duct, it weighed 4850 grams.

The surface is smooth and the organ is firm; on section it is also smooth, with bile staining. In this microscopically the cirrhosis is of the lobular type, although the islets of liver-cells are rather small. A marked feature is the comparative denseness of the newly formed fibrous tissue and the relative abundance of the newly formed bile-capillaries. Degenerative changes are also present.

In the other type the liver is small, bile-stained, and with a fairly diffuse granulation, the granulations being of medium size, but more or less even in character.

Cirrhosis from Perihepatitis (*Chronic Glissonitis*).—The liver is usually smaller than normal and much deformed; the Glisson capsule is much thickened, and may measure from 10 to 15 mm., and is of a grayish-white color, rather translucent, and usually strips readily from the organ. The liver substance is usually cirrhotic, but not invariably so. In some cases the thickening is more marked in the portal sheaths about the hilus than in the capsule. In many cases the spleen is similarly involved. The condition is really a local chronic peritonitis. Most cases give an alcoholic or syphilitic history.

Pick¹ has recently drawn attention to a form of Glissonitis—**pericarditic pseudocirrhosis**—which is associated with old pericarditis. There is usually partial or total pericardial synechia, together with adhesions between the liver and the diaphragm. Ascites may occur in such cases.

Pericellular Cirrhosis.—This variety is found more especially in connection with syphilis and tuberculosis. A striking example is also found in the so-called "Pictou cattle disease," a chronic infective cirrhosis of the liver, which has been studied especially by Wyatt Johnston and Adami.

Tuberculosis.—The occurrence of primary tuberculosis of the liver is doubtful, but as an accompaniment of tuberculosis elsewhere is frequently seen. It occurs in three forms: disseminated miliary tuberculosis, chronic tuberculous hepatitis, and as solitary tubercles.

The miliary tubercles may be so small as to be readily overlooked, particularly in a fatty liver. When visible they are present as minute gray or grayish-yellow points, often slightly bile-stained. Microscopically the tubercles are situated for the most part in the periportal connective tissue, and may project somewhat into the lobule; exceptionally they are found in the interior of the lobules (Fig. 260). Generally the foci have the appearance of lymphoid nodules with epithelioid cells and perhaps giant cells, while caseation not uncommonly occurs. In the center of the tubercle the liver-cells are destroyed, and those at the margins show atrophy and fatty changes. When bile-ducts are involved, they may simulate the appearance of giant cells, from which they must be carefully distinguished. Even when the fully formed tubercle is not present, the periportal connective tissue frequently shows a round-cell infiltration, and there may be some cirrhosis with proliferation of the bile-ducts.

¹ *Zeitschrift f. klin. Med.*, xxix., 1896.

In the second form the liver is the seat of a diffuse overgrowth of connective tissue, in which can be seen gray or grayish-yellow tuberculous nodules.

Solitary tubercles of some size, generally few in number, with central caseation, are rarely met with.

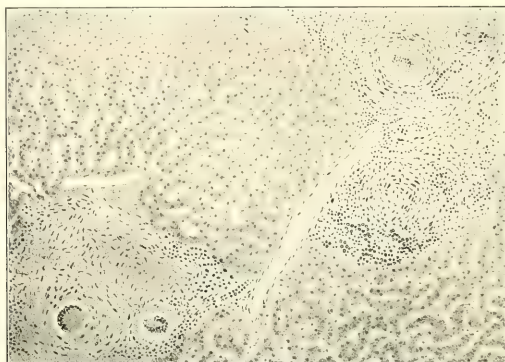


FIG. 260.—Miliary tuberculosis of the liver. $\times 72$ (Dürck).

Syphilis.—The lesions of congenital and acquired syphilis in the liver are practically identical, the only modification arising being due to the element of time and the difference in the reactive powers of the liver at different periods of life. We can recognize the following forms: 1. Acute

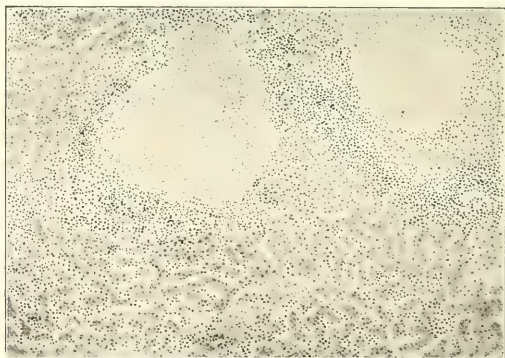


FIG. 261.—Fresh gummatous hepatitis with acquired syphilis (Dürck).

parenchymatous hepatitis (with jaundice). 2. Large, well-formed gummas. 3. Miliary gummas, often with marked fibroid change affecting circumscribed areas or the whole organ; the liver often enlarged. 4. Syphilitic cirrhosis. 5. Tumor-like outgrowths (Fig. 261).

The appearances in the first form resemble those of acute yellow atrophy.

The large gummas in a more or less advanced state of absorption and fibrosis are a common form of syphilis seen in the livers of adults, and lead to marked deformity of the organ. When the process has run its course, or nearly so, the liver is divided into numerous lobes by deep fissures, which are really fibrous scars. This is the so-called *hepar lobatum*. The scarring is usually irregular in distribution. In the usual form the gummas are multiple and scattered through the liver. On section they appear as yellowish necrotic areas surrounded by a zone of grayish-white connective tissue, which sends out radiating processes into the liver substance, which is often of a dark-brown color (Fig. 262).

Microscopically there are to be seen within these bands of fibrous tissue small collections of round cells, showing that the condition is a progressive one. The liver-cells usually show brown atrophy, or there may be amyloid

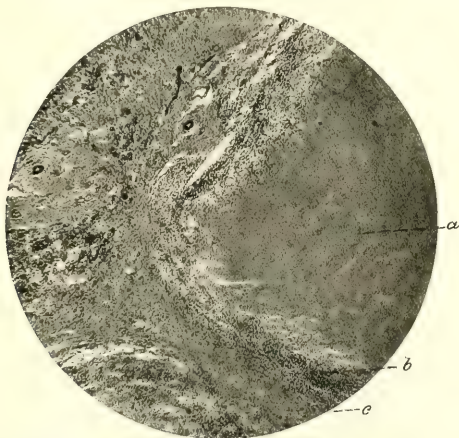


FIG. 262.—Liver—syphilitic gumma: a, gummy center; b, leukocytic infiltration; c, fibrous capsule; d, newly formed capillary. Leitz objective, No. 3.

disease. In advanced cases nothing but the scar is left, the necrotic portions having been completely absorbed (Fig. 263).

In infants a diffuse infiltration is the rule, and the type that of a pericellular cirrhosis. In the early stages there is a cellular infiltration of the intra-acinous and also of the interacinous connective tissue diffused throughout the organ. When fibrous tissue is deposited the liver is hard, somewhat enlarged, the surface smooth, or in exceptional cases finely granular. On section the color is yellow, yellowish, or reddish-brown, not unlike the color of flint. The lobules are no longer readily recognized.

Microscopically there is a periportal proliferation of fibrous tissue, which invades the lobules, destroying their structure, and containing numerous foci of round cells with newly formed bile-capillaries. The characteristic of the newly laid down connective tissue is that it is delicate and translucent, containing few nuclei, and is laid down diffusely, insinuating its way between

the liver-cells, so that they are isolated from each other or are found in little groups of two or three. There is apparently not much tendency to contract in this form (Fig. 264).

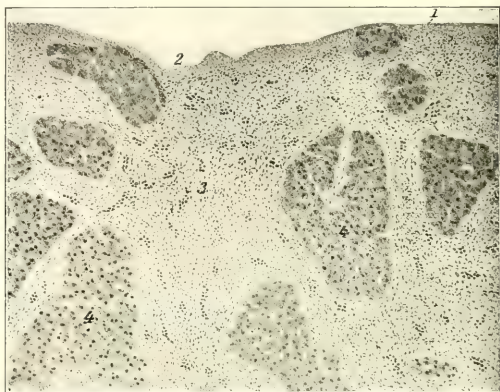


FIG. 263.—Syphilitic cirrhosis of the liver with contraction of the capsule. $\times 35$ (Dürk).

In the fifth group the masses have been mistaken for malignant growths. Microscopically they present an outer layer of liver-tissue infiltrated by

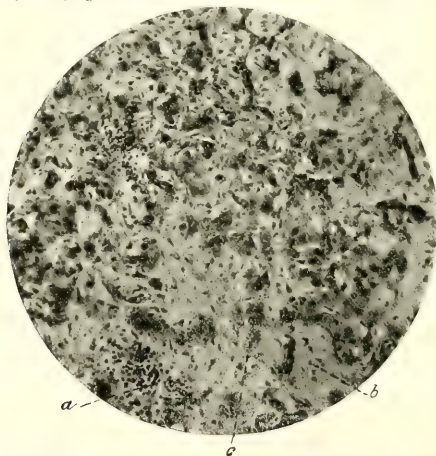


FIG. 264.—Liver—pericellular cirrhosis (syphilis): a, proliferating connective tissue; b, fully formed and very dense connective tissue; c, isolated and atrophying liver-cells. Leitz objective, No. 5.

collections of round cells enclosing a dense mass of fibrous tissue with more or less gummy degeneration. They seem to be derived from isolated

gummatous foci, with reactive new formation of liver-parenchyma about the periphery, which is infiltrated also with miliary gummas, and eventually fibrous tissue.

Actinomycosis.—Actinomycosis in the liver takes the form of numerous miliary abscesses together with larger ones, which are aggregated into lobular areas, evidently produced by the coalescing of smaller foci. With this is a proliferation of the connective tissue whereby the abscesses are separated by finer or coarser bands. When the pus is washed out the liver has a curious and characteristic spongy appearance. In the pus the fungi can be readily demonstrated. The infection is supposed to be usually from the intestine through the portal system, but in a case recorded by Moser¹ no primary focus could be discovered.

Tumors.—Tumors occur in the liver both as primary and secondary growths. The former are of both epithelial and connective-tissue origin: connective-tissue growths, with the exception of the angioma, are uncommon. It is impossible to draw a hard-and-fast line between hypertrophy and adenoma, and between the latter and carcinoma.

Of the primary tumors, the benign are the adenoma, the tubular or cyst-adenoma, angioma, fibroma, and lipoma. The first occurs in normal and cirrhotic livers, and forms single or multiple nodules of a grayish or yellowish-white or of a reddish-brown color. These microscopically consist of convoluted and branched gland-tubules or bands of liver-cells, which are not, however, grouped into the characteristic lobules. Some of the tubules may show a small lumen. According to many authors they are derived both from the liver-cells and from the bile-ducts; but according to Rindfleisch the former is the case. The adenocystoma is formed of numerous cysts or groups of cysts filled with clear fluid, and seems to be developed from outgrowth of the bile-ducts in the periportal connective tissue.

The **cavernous hemangioma** is a relatively frequent tumor, and usually occurs in the atrophic livers of elderly people. It forms a tumor of a dark-brown or purplish-red color, sharply defined from the liver-tissue, and sometimes surrounded by a fibrous capsule. When cut into blood can be squeezed out, leaving a spongy network of fibrous tissue with sometimes bands of smooth muscle. The size varies from that of a millet seed to that of an apple or even larger. The tumor is formed by a cavernous dilatation of the capillaries, with atrophy of the intervening liver-cells. Secondary proliferation of the vessel-walls and the supporting fibrous tissue takes place. The spaces can be injected from the portal vein or the hepatic artery. Thrombosis readily occurs in the cavities, with consecutive organization of the clot.

Klebs has described a lymphangioma.

Primary **carcinoma** of the liver is found under three main forms.

In the first—**cancer massif**—there is usually a single large cancer-mass, situated most frequently in the right lobe, which it may almost wholly replace. Frequently around the main mass are found several isolated nodules which represent local metastases. The cancerous material is of a whitish or whitish-yellow appearance, sometimes slightly reddened, and is of fairly firm consistency. Comparatively little cancer-juice can be scraped away. The mass is often sharply defined from the liver substance, but parts

¹ *New York Med. Jour.*, April 11, 1894.

may show infiltration. The remaining liver-tissue is compressed, atrophic, and the vessels often occluded. Large cancer-nodules often show softening and degeneration in the center, and if situated on the surface of the organ may show characteristic umbilication. General metastasis is not common.

The second type—the infiltrating **carcinomatous cirrhosis** of Perls—occurs under the picture of a nodular cirrhosis. The liver is more or less enlarged, the capsule thickened, and the surface warty. On section there are abundant bands of connective tissue to be seen, in which a few islets of liver-tissue still remain, but which contain cancer-nodules the size of a pea or larger, of a whitish or pale-red color and soft, juicy consistency. Invasion of the liver-capillaries and portal vein is not uncommon. When the nodules have apparently arisen from a pre-existing adenomatous new growth they are of a grayish-brown color, firmer, and not so juicy.

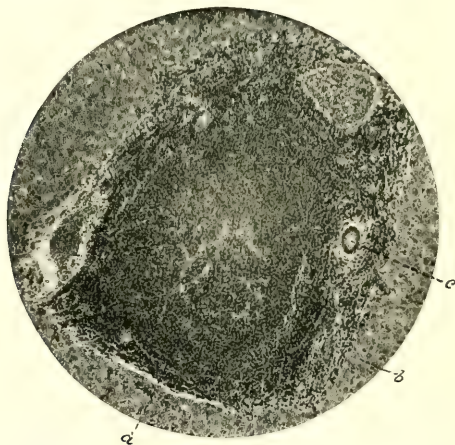


FIG. 265.—Liver—lymphosarcoma: *a*, sarcomatous nodule in the portal sheath; *b*, liver substance; *c*, bile-duct. Leitz objective, No. 5.

In the third, a rare form, there is a cancerous infiltration of Glisson's capsule, which arises from the larger bile-ducts. The nodules in the portal sheaths are closely packed, often fused, and gradually diminish in size as the finer terminations of the supporting stroma are reached. Owing to the compression of the bile-ducts icterus is common.

According to their histologic appearances we can divide the carcinomas into the cylindric-cell adenocarcinoma and the medullary form with solid cell-masses. The cancer with cirrhosis is more of a scirrhus type; but according to many observers (Hanot, Frohmann, and Ziegler) is developed in a cirrhotic liver by atypical proliferation of the adenomatous masses of the liver-cells.

Primary sarcoma is rare, and forms more or less circumscribed nodules within the liver; many of them are pigmented, and often seem to be formed

in the neighborhood of vessels. W. W. Ford¹ has recorded a case of primary sarcoma developing in a cirrhotic liver.

In lymphosarcoma there is a massing of lymphoid cells in the portal sheaths and in the intralobular capillaries. But in addition lymphomatous nodules can be seen here and there scattered throughout the organ (Fig. 265).

Block has described a melanotic endothelioma.

Secondary malignant growths arise by direct extension or by metastasis. As the new growth in the liver may attain to considerable size and may predominate the clinical picture, it is not always easy to discover the primary focus.

Carcinoma of the gall-bladder or of the bile-duct often spreads directly



FIG. 266.—Bile-cyst of the liver.

to the liver, but cancer of the pylorus only does so when there has been some previous adhesion of the stomach to the liver.

Metastases in the liver are frequent, particularly in cancerous disease of the gastro-intestinal tract, the uterus, the pancreas, the esophagus, and the larynx. They arise from small masses of cancer-cells which reach the liver as emboli either through the portal vein or the general circulation. Wherever they lodge they develop into cancer-nodules and compress and destroy the liver-tissue. They generally form multiple nodules scattered through the organ, which are at first miliary or submiliary in character, but soon fuse into masses the size of the fist or larger. When they reach the surface they often project in the form of whitish masses covered with congested serosa.

When softening and liquefaction have taken place in the center umbilication is produced. The consistence depends in general upon the character of

¹ *Am. Jour. Med. Sci.*, cxx, 413, 1900.

the original growth. On section the masses are whitish or, when degeneration is taking place, of an opaque, yellowish color, often with radiating striae. Hemorrhagic, mucinous, cystic, and calcareous degeneration have been observed. When the liver-cells are pressed upon they are reduced to flattened scales of a brownish color from pigmentation. The liver as a whole may be enormously enlarged.

Of the secondary sarcomas the pigmented are the most important. In the case of the melanotic form, next to the lung the liver is the chosen seat of metastatic deposit. This form produces either circumscribed pigmented nodules or a diffuse infiltration showing yellow, gray, or blackish-brown streaks, which give somewhat the appearance of granite to the cut section.

The hepatic capillaries may become so closely packed that ascites develops.¹ Mixed tumors are also found—fibrosarcoma and myosarcoma.

Among cysts should be mentioned bile-cysts; there is a congenital cystic liver associated with innumerable cysts in the kidneys, and blood-cysts (Fig. 266).

Parasites.—The most important are the echinococcus, the *Pentastomum denticulatum*, and the *Distoma hepaticum*. Echinococcus disease is not so frequently found in America as in Europe, but is occasionally met with in the Mennonite settlements of Manitoba and the Canadian Northwest. Echinococcus-cysts are unilocular or multilocular, and are surrounded by a laminated connective-tissue capsule. The unilocular form occurs in the form of single or multiple masses; the cyst is usually situated in the right lobe and may attain the size of a man's head. The cyst-wall is composed of a connective-tissue membrane sharply defined from the liver substance, which at the margin is by pressure converted into concentric layers of flattened liver-cells. Within the fibrous capsule is the gelatinous, transparent echinococcus-membrane, which under the microscope shows the characteristic concentric lamination. The contained fluid is clear, watery, or slightly tinted, and may contain numerous small bladders or daughter-cysts.

This fluid may by degeneration and absorption be converted into a caseous, gritty substance resembling mortar.

THE BILE-PASSAGES.

Among malformations may be mentioned absence of the gall-bladder, atresia of one or other of the passages, reduplications of the ductus communis, and opening of the single or reduplicated duct into the stomach or at an unusual point in the bowel.

Inflammation (cholangitis or cholecystitis) can be brought about by infective agents coming from the intestine or the liver itself; by extension of inflammation from neighboring parts; as a hematogenic affection; or from the presence of calculi or parasites in the bile-passages. The bacteria usually found are the *B. coli*, pus-cocci, *Diplococcus pneumoniae*, *B. typhi*, and the *B. tuberculosis*.

The affection may be simply catarrhal, or may be purulent, diphtheritic, or gangrenous. A frequent site for a simple catarrh is the common duct about the bile-papilla. The mucosa is a little swollen, but not usually reddened, and the diverticulum of Vater is occupied by a grayish, slimy, mucinous plug which leads to obstruction to the outflow of bile and conse-

¹ Herrick and Hektoen, *Am. Jour. Med. Sci.*, cxvi., 1898.

quent icterus (catarrhal jaundice). A chronic catarrh leads to thickening of the walls and a polypoid thickening of the mucosa.

In the purulent form the gall-bladder is chiefly affected, and is distended with mucus mixed with bile. The bladder is often covered externally with fibrinous exudate, and may be adherent to the neighboring viscera. In some cases perforation occurs. Abscesses of the liver or pancreas have been noted. The occurrence of suppurative cholecystitis as a complication of typhoid fever has recently attracted attention. Chiari noted that the *Bacillus typhi* was able to live in the bile-passages for months after apparent cure of the typhoid cases. This fact may possibly explain some cases of reinfection. Fistulous communications with the hollow viscera or the external air can occur.

Biliary calculi are of three kinds—pure or almost pure cholesterin, those formed of bilirubin calcium, and mixed forms.

Stones are formed more than twice as frequently in females as in males, and generally after middle life. Stagnation of the bile seems to be an important predisposing cause. This probably leads to absorption of the alkaline salts and the formation of an acid bile, which favors the development of various bacteria, notably *B. coli* and *B. typhi*. Thus, a slight chronic catarrh is the result which leads to an increased outpouring of mucus, in which the bile-pigments and calcium salts are precipitated. The calculi may be single or multiple; Otto reports a case in which there were 7802.

When the stone is in the cystic duct the gall-bladder is usually thin-walled, the mucosa being replaced by a fibrous layer of a dense, white appearance, and contains fluid of a limpid appearance like water. Calculi in the gall-bladder may cause catarrhal or suppurative cholecystitis, with even necrosis and perforation. Fistulous communications are thus sometimes met with. According to Courvoisier, communication with the exterior is the commonest event; but Strümpell and Murchison agree that cholecysticoduodenal fistula is the most frequent. An extremely rare form is the cholecysticogastric, an example of which we had an opportunity of recording.¹

Calculi in the common or hepatic ducts may lead to complete obstruction, with the production of jaundice, dilatation and fibrosis of the ducts, and inflammatory and cirrhotic changes in the liver and pancreas. Obstruction, however, can be produced by other causes, such as secretion within the ducts, tumors, cicatricial contractions, or pressure from without.

One result of the presence of gall-stones should not be forgotten—**carcinoma**—which may spread by continuity to the liver, so that the point of origin may at last be difficult to make out. It is usually of the cylindrical-cell type. Sarcomas, fibromas, and myxomas are recorded.

THE PANCREAS.

The pancreas is a glandular organ made up of a collection of lobules, held together loosely by fibrous tissue. The general appearance resembles that of a salivary gland, hence the Germans call it the "*Bauchspeicheldrüse*"; it differs from the latter, however, in the fact that the secreting cells are more granular, and there are in addition small masses of somewhat flatter cells, the so-called "*cell collections*" of Langerhans.

¹ *Montreal Med. Jour.*, November, 1898.

The connective tissue is loose, frequently containing a considerable amount of fat-cells together with lymphoid tissue, blood-vessels, nerves, and ducts. The looseness of the supporting structure is often increased by the fact that in stout and well-nourished persons the pancreas is surrounded by much fat, which infiltrates the gland extensively, thus separating the lobules widely. This looseness of the stroma renders the organ readily liable to undergo vascular changes, edema, hemorrhage, blood imbibition, and the like. The nature of this interstitial tissue, further, has an important bearing upon the subject of fat-necrosis and inflammation.

Another important point is that the organ secretes a digestive fluid, which under certain conditions acts upon the tissue of the gland, and even during life may bring about serious trouble, and after death may rapidly mask pathologic change. It seems impossible to deny that, just as in the case of digestion erosions of the stomach and esophagus, the condition of self-digestion occurs as an agonal manifestation in some cases, or even some time before death. As a postmortem manifestation it is, of course, much commoner. The appearance of the organ in this condition is peculiar: the pancreas has often a dead-white, sometimes glazed, appearance. Microscopically there are all grades, from very slight scattered areas of degeneration, as evidenced by loss of staining power and the obscuring of the nuclei, up to a point where the whole section presents the appearance of a glassy mass staining intensely with eosin, in which no nuclei appear and only the lobules and ducts serve to indicate the true nature of the organ. In the milder conditions the nuclei appear more resistant, and are present as small pigmented particles, while the outlines of the cells are lost. The condition was first adequately described by Chiari, who attributed it to the action of the digestive ferment, and called the condition "self-digestion." It is common; of 210 pancreatic sections we have examined, it was present in 63 per cent.

One would expect that the longer the time that had elapsed after death the more advanced would be the condition. While this is in general true, other factors enter into the process. We have observed that extensive self-digestion has been present when the autopsy was performed so soon as three hours after death; while, on the contrary, at the end of thirty to forty-eight hours the condition may not be at all marked. This leads us to think that much depends upon the physiologic activity of the gland at the time of death. If the acini be loaded with the ferment, we would expect rapid digestion; while, on the other hand, where the ferment had been discharged, self-digestion has been retarded. We should not forget also in this connection, as in the case of other glands and in the epithelial structures, that death does not at once put an end to secretory activity, so that if at the moment of death the gland should be empty, yet in the course of a few hours secretion might again take place.

The other factors that might be mentioned are the degree of acidity of the duodenal contents. There is no doubt that fluids and certain processes can extend up the pancreatic duct and thus modify the existing conditions. Lastly, the question of bodily heat and external temperature would have much to do in the production of the condition.

It is important to bear in mind the position of the pancreas. It lies behind the stomach, in close proximity to it and to the lesser peritoneal cavity; the head more or less completely surrounds the duodenum; the tail touches

the spleen; posteriorly is the celiac plexus; farther away, but still near enough to be of importance, are the kidneys. The common bile-duct runs for the latter part of its course through the head of the pancreas, and opens into the duodenum either in common with or in close proximity to the pancreatic duct. Thus, inflammation of the duodenum and the bile-passages, calculi, and tumors about the liver and bile-channels may seriously affect the pancreas. Ulcers of the stomach sometimes extend into the pancreas, leading to local suppuration and often to fibroid changes. Disease of the spleen and the left kidney, particularly suppuration, may extend to the pancreas; and, finally, suppuration of the pancreas may rupture into the duodenum, stomach, lesser peritoneum, or the abdominal cavity.

When we consider the pancreas from the point of view of its physiologic functions, which are, as we know, of the highest importance, it is not surprising that it should have been the subject of innumerable studies. Still, it must be said that all this work, while it has called attention to certain phases of the subject, has left the whole question of pancreatic disease, but particularly pancreatic inflammation and hemorrhage, in a very disorderly and confusing state. Many of the studies have been made from the standpoint of the clinician and the surgeon, very frequently to the neglect of the pathologic and histologic aspects of the case. As an example of this, take the subject of hemorrhagic pancreatitis. Cases of this are being recorded almost every week, and yet it is not often clear whether these cases are truly related to inflammation at all, or whether they should be classed with vascular or degenerative disturbances. The clinicians have performed an important duty in pointing out a suggestive train of symptoms associated with diseases of the pancreas, but the scientific classification of the morbid conditions producing these symptoms has yet to be made.

The affections of the pancreas are, with a few notable exceptions, of comparatively little importance, and bear in many ways a striking resemblance to those of the salivary glands, particularly the parotid. It is striking, however, that cartilaginous tumors which are so prominent in the parotid gland are wholly wanting in the case of the pancreas—an argument in favor of the view that they are due to some local peculiarity of structure or development.

Physiologically the pancreas is of great importance. Its secretion is the most powerful of the digestive fluids. There is also considerable evidence in favor of the view that it also has an internal secretion, serious interference with which leads to the production of glycosuria.

The action of the pancreatic secretion is to change proteids into peptones, and then into leucin and tyrosin, from which by fermentation are produced phenol, skatol, and indol.

The serious affections of the organ, then, may lead to rapid emaciation, due to the interference with nutrition, or to a diminution of indol with a diminished indican excretion by the urine, and sometimes glycosuria; fat may also appear in the stools.

Other symptoms sometimes seen in pancreatic disorders are intense abdominal pain, vomiting, slow heart action, and collapse, all of which are attributable to involvement of the celiac plexus of nerves. Catarrh of the duct generally is associated with duodenitis and cholangitis, so that slight grades of jaundice are not infrequent. While, as a rule, marked pancreatic disturbance is sooner or later fatal, it should not be forgotten that a com-

pensatory action takes place occasionally, and it has been suggested that the stomach and the Brunner glands of the duodenum may act vicariously. One case is on record in which a patient lived for years after the whole, or at least the greater part, of the pancreas had sloughed away.

Malformations.—Complete absence of the pancreas is found only in fetuses which show other serious defects. A portion of the head may be separated from the rest and form a lesser pancreas, which lies upon the anterior surface of the duodenum. The excretory duct may unite with the duct of Wirsung or may discharge into the duodenum by a separate opening. The pancreas may be divided into two equal or unequal parts connected together by the pancreatic duct. More frequent is an accessory pancreas, which is found in the stomach, duodenum, or jejunum, situated in the submucosa or muscular coat.¹ The pancreatic duct may discharge into the stomach or at an unusual point in the duodenum. Accessory spleens are sometimes found embedded in the head or the tail of the pancreas. An interesting though rare anomaly of the pancreas is the so-called *pancreas annulare*. In this case the head of the pancreas forms a ring around the duodenum, which may be constricted.

Retrogressive Changes.—Fat-necrosis.—This affection is characterized by the presence of areas of degeneration, varying in size from that of a pin-head to that of a pea or even larger, scattered through the pancreas, the omentum, or indeed through the fatty structures, to a considerable distance from the pancreas. These areas are of a dead-white color, or may be soft or with gritty centers; they are sometimes surrounded by a hemorrhagic or inflammatory zone, but not invariably. When in the pancreas they are seen in the interstitial substance, and the necrotic areas may soften, giving rise to cysts. Cases are on record, however, in which the spots were in the omentum, while the pancreas was free. Cases are generally associated with acute or chronic inflammation of the pancreas, tumors or obstruction of the duct. Whether fat-necrosis is to be regarded as the cause or the effect of the inflammatory process is not yet settled.

The researches of Hildebrand and Flexner have proved that the condition is due to a liberation of the fat-splitting ferment of the pancreas, which acts upon the fat-cells in the pancreas and its neighborhood, converting the fats first into fatty acids, and next into salts formed from the combination of the fatty acids with calcium. Advanced cases may be associated with severe pancreatic hemorrhage or the sequestration of large portions of pancreatic tissue, so that rapid death not infrequently results.

Atrophy.—Simple atrophy occurs as a senile manifestation and in marasmus from infection or chronic disease. The pancreas is small, shrunken, and cylindric in section, and the surrounding fat is diminished. On section the organ is of moderate or increased resistance; the lobules are small, so that the interstitial connective tissue appears increased, although it may be actually diminished.

In many cases of diabetes the pancreas is found atrophic, but differs somewhat in appearance from that in simple atrophy. The organ is often small, flabby, and relaxed; in color it is brownish, and rather flat on cross-section. There is often a compensatory increase of fat in the neighborhood. Microscopically the atrophy is found to affect the secreting structure, while the interstitial stroma with the blood-vessels is distinctly increased; there

¹ See Nicholls, *Montreal Med. Jour.*, Dec., 1900.

is in addition an infiltration of round cells, which is seen generally at the periphery of the lobule and extending some little way in (Fig. 267).

When atrophy of the pancreas is extreme fatty globules and crystals appear in the feces. According to Demme and Biedert, the fat-diarrheas of children are associated with atrophy and fibrosis of the organ.

The recent interesting researches of Opie¹ show that in diabetes there may be chronic degenerative lesions involving the islands of Langerhans only.

Fatty change in which small particles of fat appear in the secreting cells is common. It occurs in infectious fevers, poisoning from mineral salts, and in inflammation of the organ.

Fatty infiltration occurs in general obesity. The organ on section is seen to contain large flakes of fat, separating widely the lobules of the

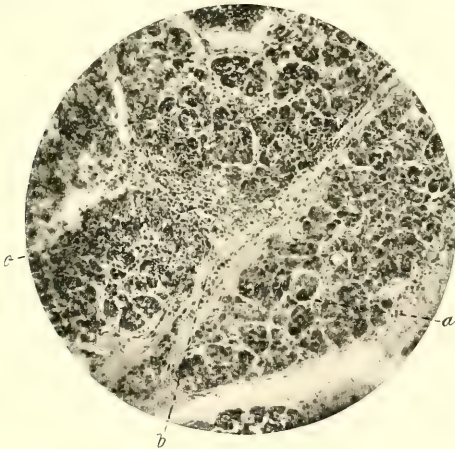


FIG. 267.—Pancreatic diabetes: *a*, atrophic pancreatic lobule; *b*, fibrous septum; *c*, round-cell infiltration. Leitz objective, No. 5.

gland, which may be markedly atrophic; fatal hemorrhage may supervene upon this condition.

Circulatory Disturbances.—**Hyperemia** and **anemia** of the pancreas are unimportant. It may, however, be mentioned that hyperemia is frequently observed in cases of pernicious anemia.

Hemorrhage.—Small hemorrhages occur in the course of infectious fevers, scorbutus, or in passive congestion. A much more important form is that in which the whole or greater part of the organ and perhaps the neighboring cellular tissue are infarcted with blood. These are the cases known as *hemorrhagic pancreatitis*. Not all cases are due to inflammation, however; among other causes may be mentioned sclerosis of the vessels, fatty degeneration of the vessel-walls, and infarction. Some cases show evidence of being of the nature of a chronic inflammatory disturbance, for we find in places, besides the fresh blood, old brown blood-pigment,

¹ *Jour. Exp. Med.*, v., 1901.

pointing to recurrent hemorrhages, and with this leukocytic infiltration and productive fibrosis. Local hemorrhages may discharge into the lesser peritoneal cavity, or may be softened and absorbed, leading to the production of cysts.

Hemorrhagic pancreatitis is found oftener in alcoholics or obese persons, and usually in those over thirty. There may be a history of dyspeptic attacks. The attack comes on suddenly, with intense pain in the epigastrium, radiating in various directions; nausea and vomiting set in, and the abdomen becomes rigid and tympanitic. Constipation is the rule. The temperature may be moderately elevated, and the patient dies collapsed in from two to four days. Cases have been mistaken for intestinal obstruction.

The pancreas is found to be firm and densely infiltrated with blood, sometimes in large clots. The neighboring cellular tissue, the omentum, the root of the mesentery, and the lesser peritoneal cavity may contain blood. Many cases are associated with gangrene of the organ or extensive fat-necrosis. Death takes place probably from pressure upon the celiac axis, as suggested by von Zenker, or from shock. The nerve-cells of the semilunar ganglia have been found degenerated with an interstitial leukocytic infiltration.

Inflammations.—Inflammation is not very common: in the 210 organs of which we have notes, acute inflammatory changes were present in 6, and in only 1 of these was the condition the cause of death. Most of the cases are complications of other disorders, and probably many more would be heard of if the pancreas were systematically examined.

Acute inflammations of the pancreas are due to infectious organisms—staphylococci, *B. coli*, *B. typhi*, and the like; and arise in three ways: 1. Hematogenic. 2. By extension from neighboring organs. 3. Through the excretory duct.

The hematogenic form is seen as a manifestation of septicopyemia, and is not common.

Ulcers of the stomach and duodenum, and suppurative inflammation of the spleen and left kidney, lead sometimes to involvement of the pancreas. When the process heals fibrous scars may be produced.

By far the commonest cause of inflammation is infection passing up the duct of Wirsung.

The following classification of acute inflammation, though based perhaps upon too limited experience, is suggested as a convenient one:

Acute.

SIMPLE.	{	Parenchymatous pancreatitis (degenerative).
		Catarrh of the ducts (sialodochitis pancreatica).
SUPPURATIVE.	{	Diffuse suppurative pancreatitis.
		Local suppurative pancreatitis (abscess).
		Pancreatitis with obstruction.
		Pancreatitis with hemorrhage (acute hemorrhagic pancreatitis).
		Gangrenous pancreatitis.
	{	Pancreatitis per extensionem.
SPECIFIC.		Miliary tuberculosis.

Chronic.

SIMPLE OR SUPPURATIVE.	{	Catarrh of the ducts.
		Diffuse productive pancreatitis.
		Diffuse productive pancreatitis with calculi.
		Productive pancreatitis with cyst formation.
		Local fibrosis.
SPECIFIC . . .	{	Caseous tuberculosis.
		Syphilis.

Degenerative parenchymatous pancreatitis occurs, according to Orth, in the infections, as typhoid fever, variola, and pyemia; but we have never met with the condition. The pancreas is swollen; at first reddened, later of a whitish or grayish-yellow color. Microscopically the parenchyma shows cloudy swelling with fatty degeneration and necrosis. In a case reported by E. Fränkel the gland was sprinkled throughout with small cavities containing a fatty granular material derived from the degenerating cells, while in the interstitial tissue there was a round-cell infiltration.

Much more important pathologically and clinically are those cases in which there is a **suppurative inflammation** caused by extension of infective agents up the duct. As the pancreatic and common bile-ducts empty usually together into the duodenum, any inflammatory process in the duodenum, bile-passages, or both, is apt to extend to the pancreas.

The symptoms are usually acute, and resemble those of hemorrhagic pancreatitis. The cases are mostly in young adult males, and usually terminate fatally in from two to four days; but in certain cases which become chronic life may be prolonged a year or more.

In an instructive case occurring in the practice of D. P. Anderson, of Montreal, in which the diagnosis was made during life, a healthy-looking, athletic young man, who gave the history of a dyspeptic attack a year previously, after a hearty supper of oysters was seized with severe gastric pain; nausea and vomiting set in, the abdomen was tender, rigid, and tympanitic, and the temperature slightly elevated. Collapse with slight icterus set in, and death followed in fifty-six hours. At the autopsy the pancreas was hyperemic, much swollen, and very juicy. Here and there minute abscesses, from which thin seropus could be squeezed out, were seen. There was no fat-necrosis or hemorrhage. The duodenum was the seat of a diffuse and severe phlegmonous inflammation. The gall-bladder contained two small bile-pigment calculi. Microscopically the liver showed an acute interstitial hepatitis. The pancreas showed marked parenchymatous degeneration, the secreting cells staining poorly and containing droplets of fat. The ducts were full of purulent secretion and the interstitial substance was diffusely infiltrated with leukocytes, which in places were aggregated within the lobules to form abscesses. Here the presence of gall-stones pointed to a persistent catarrhal cholangitis, probably associated with a slight duodenitis, which had been aggravated by overeating.

In all such cases we have examined there has been a duodenal catarrh, and in most an acute interstitial hepatitis, so that the etiology would seem clear. The symptoms above mentioned, especially when occurring in a presumably healthy young man, should always arouse suspicion of pancreatic disease. Most cases are mistaken for intestinal obstruction, biliary colic, or gastric ulcer.

In this case the pancreatic duct, while inflamed, was not occluded; but we have seen one case, apparently unique, in which from obstruction the acini were converted into rounded cavities lined with flattened cells, recalling the analogous dilatation of the tubules in chronic interstitial nephritis.

Pancreatic abscesses may burst into the peritoneum, causing septic peritonitis, or may form fistulous communications with the stomach or intestine. In a case recorded by Chiari¹ the sequestered pancreas was passed per anum with complete recovery.

Diffuse productive pancreatitis is characterized by a proliferation of the interstitial connective tissue, often with associated atrophy of the secreting structure, whereby the whole organ becomes hard and may simulate a tumor.

The most frequent causes are repeated or prolonged inflammatory disturbance, obstruction to the free outflow of the secretion, inflammation of the neighboring structures, or syphilis. When the duct is obstructed by a fibrous contraction or the presence of calculi the duct becomes dilated, often to the size of a finger, and the whole organ is converted into a fibrous mass in which very little glandular tissue can be recognized.

The stones are produced in the first instance by a catarrh of the ducts, but their presence excites a chronic productive inflammation which may totally destroy the function of the organ. In such cases glycosuria is a prominent feature. Pancreatic calculi are rounded or elongated, of a whitish or grayish-brown color, and may be single or multiple. They may be minute or reach the size of a walnut; their composition is usually carbonate of lime. Besides fibrosis, suppuration of the gland, cyst formation, or cancer can occur.

Tuberculosis, on the whole, is rare. Disseminated miliary tuberculosis is recorded; but more common is the solitary caseous focus. One case of primary caseous tuberculosis is reported by Sendler; but nearly all cases are due to extension of tuberculous processes from the neighboring glands. In the pancreas itself it is the lymphoid nodules which are chiefly affected. Still, it is surprising how frequently the pancreas escapes, for it may be completely surrounded by tuberculous masses without itself giving any evidence of tuberculous disease.

Syphilis leads to a fibrosis of either the whole organ or the head only; the surface is smooth, dark colored, and the tissue firm. Diffuse interstitial pancreatitis is rather frequent in congenital syphilis.

Tumors.—Carcinoma is by far the most frequent primary tumor; it is usually of the scirrhus type, and is commonly situated in the head of the organ. Medullary and colloid cancers are occasionally found. Carcinoma of the body or the tail is uncommon. Where the new growth involves the common bile-duct icterus results, and when the pancreatic duct is occluded the unaffected portion of the gland may form a cyst.

Primary sarcoma usually is found in the head or tail of the organ. It is rare, but several cases have been recorded recently.

Lymphosarcoma.—Not much is known of this condition as yet; in the only case we have seen the pancreas was much enlarged, and nodules of new growth of a soft, white appearance were found between the lobules. Microscopically there was a diffuse infiltration of the capsule with lymphoid cells, and everywhere in the interstitial substance the lymphoid cells were abundant.

¹ *Wien. med. Woch.*, 1876 and 1880.

Secondary sarcoma is not uncommon, and the primary focus is generally in the duodenum, stomach, or bile-ducts.

THE PERITONEUM.

(Omentum, Mesentery, and Abdominal Wall.)

As in the case of the other serous sacs, the great majority of peritoneal affections are due to disturbances of the various organs which it invests. The most frequent offender in this way is the digestive tract; next, the liver and the portal system; and then the female genital apparatus. An intimate relationship thus exists between the abdominal viscera and this membrane, and by far the most important class of disorders is the inflammations that are due to the action of different germs; these inflammatory processes in character and intensity depend largely upon the nature of the invading organism. The extension of the process is in many cases assisted by the frequent movements of the intestines, or modified and localized by the agency of the great omentum and by adhesions.

The peritoneum is a membrane composed of delicate connective tissue containing elastic fibrillæ and covered by a layer of endothelial cells. In the deeper layers are the lymphatics and blood-vessels, the former being in communication with the abdominal cavity, which is thus to be regarded as a large lymph-space.

Of the manner in which the peritoneum invests the various viscera, nothing need be said here, but a particular reflection of it—the great omentum—demands a word.

The great omentum, that organ which was so full of omen to the Roman augurs, has attracted remarkably little attention since the time of these priestly comparative pathologists. This is probably due to the fact that, being a variable organ, at least almost absent, it was looked upon as of comparatively little use.

There is reason, however, for thinking that while its functions are few, they are of considerable practical importance. The great omentum is composed of a double layer of the peritoneal membrane folded upon itself, and is thus composed of nothing but connective tissue and endothelial cells. It is more or less loaded with fat, but its chief characteristic is its remarkable vascularity. The vascular supply is altogether in excess of the needs of the structure itself, and this fact probably gives us the clue to the omentum's part in the animal economy. There is then a rich network of delicate vessels, which are separated from the peritoneal cavity by only a delicate layer of cells. Hence it is possible that one function of the omentum is the transudation of plasma or lymph into the abdominal cavity, or the absorption of that which is already there, and this largely under the control of the nervous system. We have thus a sort of nervous heart in the abdominal cavity which keeps up an imperfect form of circulation. This fact is of importance in connection with the development of ascites.

Malpighi was perhaps the first to make the definite suggestion that fluid may be poured out through the omental vessels, and thus be a cause of dropsy.

Landgraf¹ cites a case of cardiac disease with ascites which was intractable after fourteen tapings. Being on one occasion compelled to perform

¹ *Deut. Arch. f. klin. Med.*, 1870.

paracentesis hurriedly, he did it with a lancet and a piece of tubing. Consequent upon this there developed a hernia of the great omentum, the size of a walnut. The protruding part sloughed away, and in a few days the ascites came to an end, and after one more tapping never returned. This case certainly suggests that the great omentum is largely responsible for the transudation of ascitic fluid. J. F. W. Ross,¹ of Toronto, has come to the same conclusion.

Besides this function of the omentum, we owe to Aristotle and Galen the view commonly accepted to-day, that the membrane is useful "to preserve the innate heat of the body"; this, it is possible, is partly correct, for it is conceivable enough that when the surface of the body is chilled the splanchnic and omental vessels are distended, and thus a warm, congested membrane is interposed between the cooled surface and the intestines.

Malformations.—Lawson Tait² has recorded a case in which the mesentery was completely absent, and in which the peritoneum covered only a small portion of the circumference of the bowels, but passed directly from one coil to another. The mesentery may be abnormally long or short, or may present fissures which are of great practical importance, since coils of intestine may be prolapsed through the opening and the lumen thus become obstructed.

Pocket-like diverticula, abnormal folds and duplications, and persistence of the inguinal canals, are not uncommon. The great omentum varies much in size and, it is said, may be almost completely absent. Partial defects are more common.

Circulatory Disturbances.—As the peritoneum is in intimate relationship with so many of the viscera, it will be readily understood that in consequence of disorders of the various organs local circulatory disturbances are easily brought about. Among such may be mentioned particularly inflammation of the gastro-intestinal tract, hernias, obstruction, and tumors. General **active hyperemia** is seen as a consequence of sudden diminution of intra-abdominal pressure, such as results from removal of a tumor or ascitic fluid, and in the first stage of inflammation.

General **passive congestion** is the result of obstruction to the portal circulation either through the liver or indirectly through the lungs or heart. In such cases the vessels of the great omentum, stomach, and intestines are markedly distended. Long-standing cases lead to an outpouring of fluid into the peritoneal cavity (hydrops peritonei or ascites). The character of the fluid is not always the same. Usually it is clear, watery, slightly yellowish, or it may contain blood-pigment or bile. Frequently here and there lying upon the coils of intestines are soft, gelatinous clots or fibrin, or veil-like shreds of endothelium.

In some cases the fluid is white and milky, with a pearly opalescence. This opalescence is due to an admixture of fat, derived either from fattily degenerated cells or from the chyle. In the latter form—**chylous ascites**—there is rupture of the thoracic duct or of the other lymph-channels, which allows the chyle to pass directly into the peritoneal cavity. In the former case, owing to chronic peritonitis or carcinoma of the omentum and mesentery, the chyle-vessels are obstructed and a clear fluid passes out, but devoid of much fat, the more solid particles of the chyle remaining behind—**pseudo-chylous ascites**.

¹ *Am. Jour. of Obstet.*, xxviii., 1893.

² *Dublin Quart. Jour. of Med. Sci.*, 1869.

Ascitic fluid may be free in the peritoneal cavity, or from adhesions may be sacculated. In children the fluid often collects between the layers of the great omentum—hydrops omenti.

The amount of fluid may lead to great distention of the abdomen, pressure upon the various viscera, together with an upward dislocation of the diaphragm, which may thus press upon the thoracic organs and seriously hamper circulation and respiration.

With regard to **hemorrhage**, we must distinguish between effusions of blood into the peritoneal cavity and hemorrhages into the tissues.

Petechiæ or small ecchymoses occur in all forms of active or passive congestion, in sepsis, the various infections, and in the hemorrhagic diathesis. Effusions of blood occur, as a rule, from tearing of the various organs (liver, spleen), the rupture of an aneurysm or a tubal pregnancy, or as a result of operations. Large effusions usually lead to death, while small areas may be reabsorbed, leaving the peritoneal surface of a blackish-brown color, owing to the action of the sulphuretted hydrogen from the intestines upon the iron of the blood-pigment.

Inflammations.—The inflammations of the peritoneum bear a general resemblance to those of the other serous membranes, but tend to be, on the whole, purulent or fibrinopurulent rather than fibrinous or serofibrinous; this is accounted for by the fact that the condition is generally due to septic micro-organisms.

There are, however, mild forms of peritonitis, particularly those which supervene upon passive congestion and ascites, and the more chronic forms, which are of the fibrinous type.

In the first stage there is congestion of the membrane, which is most marked where the coils of the intestines come into contact. A little later the intestinal walls are slightly matted, the serous surface is dull and lusterless, and there are delicate threads of fibrin at the points of contact, giving the membrane a somewhat granular appearance. In some forms the exudate is thicker and of a yellowish flaky character. There may be relatively little fluid outpoured, but in some cases there is a turbid purulent fluid containing rather large yellowish flakes which are soft and pulpy. In such cases the flakes tend to sink to the dependent portions (pelvis, flanks), or to collect about the liver and spleen.

In cases which are less acute and tend to become chronic, with little fluid exudate, small pockets of thick yellowish-green pus are often found. In certain cases these pus collections seem to be partly absorbed and undergo inspissation, and may even become calcified and surrounded by fibrous adhesions. In other cases the pus may burrow through the intestinal wall and perforation ensue.

A common and malignant form of peritonitis is that dependent upon perforation or rupture of the intestinal wall, in which the exudate is feculent as well as purulent. The exudate in these cases is foul-smelling and of a brownish color, due to the presence of particles of fecal matter. The intestines in peritonitis are usually much distended, owing to muscular paralysis.

The character of the inflammation depends largely upon the nature of the infecting germs. The purulent exudates are due to staphylococci, streptococci, the colon bacillus, and the *Diplococcus lanceolatus*. The inflammations excited by *B. tuberculosis* and the gonococcus tend to be more chronic and subchronic.

It is noteworthy that when *B. coli*, *B. tuberculosis*, and the gonococcus are the offenders, plastic or fibrous adhesions are apt to form, while in the case of typhoid fever there is very little attempt at reparative adhesion. One case has come under our notice, however, in which the omentum was found adherent to a perforated typhoid ulcer, thus preventing general peritonitis; but such instances are rare.

Durham, in a valuable contribution "On the Mechanism of Reaction to Peritoneal Infections,"¹ calls attention to an important function of the omentum in peritoneal inflammations. In experimental animals he has observed that up to the end of one hour after intraperitoneal injection of bacteria the peritoneal fluid contains relatively few cells, and has found that this leukopenia is due in the main to attachment of the free cells to the surface of the great omentum. In animals which had died or had been killed twenty-four to forty-eight hours after injection with an efficient but not too great a number of bacteria, the peritoneal fluid was found to be sterile to culture, but the omentum gave a vigorous growth.

These observations throw light upon those clinical cases of peritonitis in which, contrary to expectation, cultures from the peritoneal fluid remain sterile. A few of the free cells are found attached to other portions of the peritoneal membrane, or escape by lymph-paths, or in the female through the Fallopian tubes, but their number is inconsiderable.

Issaëff has also brought out a point which may be of use clinically, that intraperitoneal injections of saline solution or serum seem to confer a power of relative immunity to infection, which, however, disappears in four to five days.

Adami,² in the most recent communication we have seen upon "The Great Omentum," points out the important part played by the omentum in peritoneal inflammation, and refers to the great rapidity with which the omentum applies itself to inflamed areas and becomes adherent by plastic and later fibroid adhesions. This he attributes to the presence of leukocytes in great masses upon the surface of the omentum, which is the source of the fibrinous exudate produced. The importance of this fact is seen in the well-known observation how frequently the omentum saves the situation and prevents a general peritonitis.

The omentum may become adherent to any of the abdominal viscera and to the abdominal wall, the latter event being frequently seen in connection with penetrating wounds of the abdominal wall.

Dunham's observation, that in peritonitis the omentum becomes rolled and folded up, does not seem to hold for many cases of peritonitis in the human subject. When such a condition occurs, it seems to indicate that the patient has been on his back for some little time.

With regard to the etiology of acute peritonitis, the work of Grawitz, and the valuable studies of Flexner,³ have done much to relieve the subject from obscurity. Grawitz divides peritonitis into primary and secondary forms. The first is the so-called "idiopathic" or "rheumatic" form. Grawitz regards all these as due to micro-organisms; but thinks that in addition to the presence of bacteria a predisposing cause, injury to the peritoneum, is necessary. In our opinion, the chemical theory of Tavel and Lanz must now be given up.

Flexner defines primary peritonitis as "A condition in which the inflam-

¹ *Jour. of Path. and Bac.*, iv., 338, 1897.

² *Phil. Med. Jour.*, Feb. 26, 1898.

³ *Ibid.*, Nov. 12, 1898.

mation, usually diffuse, of the serous cavity takes place, without the mediation of any of its contained organs, and independently of any surgical operation upon these parts."

Primary peritonitis is due to micro-organisms which reach the membrane through the blood-stream or the lymph-channels. It is conceivable that bacteria may pass through an intact intestinal wall, but this is as yet by no means proved. In some cases of complicating peritonitis, such as that seen associated with ascites, such an occurrence is, however, probable.

Of 106 cases of peritonitis (not including tuberculous cases) studied by Flexner, 12 were primary; micro-organisms were found in 10 cases, of which 9 cases showed but a single form of germ. In such cases the portals of entry may be various; an inflammatory focus in almost any part of the body may be a starting point.

Flexner divides the secondary peritonitides into "exogenous" and "endogenous." In the former we have examples of wound infection, the bacteria having in large part entered from without.

Of 34 cases cited, 25 were single and 9 multiple infections. The germ most frequently found was the *Staphylococcus aureus*, and next to that the *Streptococcus pyogenes*. The *B. coli* when present was generally associated with these germs.

In the "endogenous" form, that in which the infecting germs come from the intestinal tract, the infection is usually multiple, and the *B. coli* was most frequently found; next to that the *Streptococcus pyogenes*, and then both combined.

As Flexner correctly points out, the few instances of primary peritonitis which do occur are really examples of terminal infection.

Besides the germs mentioned as the cause of the infection, it may be stated that several instances have been recorded recently of peritonitis due to a pure growth of the gonococcus, which had apparently gained entrance through the Fallopian tubes.

Of the various intestinal lesions which are the cause of peritonitis, the most frequent are appendicitis and other forms of intestinal perforation, strangulated hernia, intestinal obstruction, and the dysenteries.

A special form of peritonitis, the **acute hemorrhagic**, which is analogous to internal hemorrhagic pachymeningitis, should be mentioned; several cases have been recorded recently. These seem to be due to a subacute inflammation in which abundant new capillary blood-vessels are formed that readily rupture; a sort of vascular membrane is thus produced. The condition may lead to considerable outpouring of blood into the abdominal cavity. Another form of hemorrhagic peritonitis is sometimes seen in tuberculosis or carcinomatosis of the peritoneum.

Chronic productive inflammation can succeed an exudative one, and leads to thickening of the serous membrane and adhesions. It is generally a local condition, and is seen in the mesentery, the great omentum, and in association with hernia; some cases are associated with tuberculosis, syphilis, and carcinoma.

Chronic perisplenitis and perihepatitis have already been referred to.

The most important type is the **tuberculous**. This can occur under various forms. A common variety is that in which small tubercles are found scattered over both layers of the peritoneum, chiefly along the course of the blood-vessels; this may be part of a general miliary tuberculosis.

Another form is that in which the tuberculous process is associated with the production of a serofibrinous exudate, which may become partially organized or undergo hyaline change. This results in great thickening of the membrane, with adhesions. The viscera are covered with a layer from 10 to 15 mm. thick, which has a pearly, celluloid-like appearance, very firm, with caseous masses throughout its substance. With this the pleura and pericardium are often similarly affected, while the viscera are relatively free from tuberculosis.

The infection may be a hematogenous or lymphatic one, or may arise by extension from the pleural cavity, the intestines, or the Fallopian tubes.

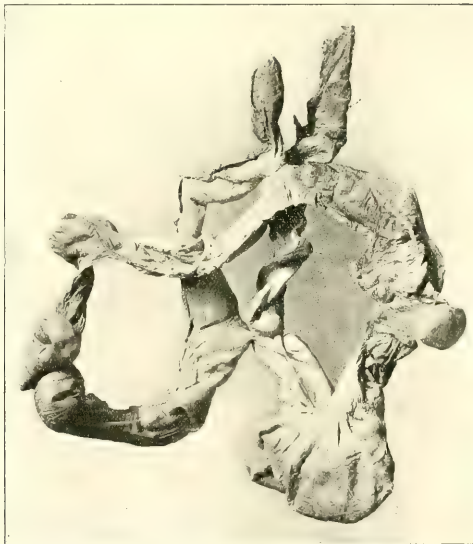


FIG. 268.—Peritoneal adhesions between coils of intestine.

It is worthy of note that tuberculosis of the peritoneum is a not infrequent complication of cirrhosis of the liver.¹

Tumors.—Of primary tumors, may be mentioned lipomas, which are found in the omentum or are derived from the appendices epiploicæ; fibromas, myxomas, and hemangiomas. Many of these forms start in the retroperitoneal tissues, particularly about the root of the mesentery.

The most important is the retroperitoneal lipoma, which is usually a combination of fibrous, fatty, and mucoid tissue, and has a distinct tendency to become sarcomatous. This forms a large fluctuating tumor which simulates ascitic fluid, and often the mistake is only discovered on the attempt to tap. A coil of intestine often can be made out crossing the tumor in front.

¹ For an exhaustive résumé of the literature on Peritonitis, see von Brunn, *Centralbl. f. allg. Path. u. path. Anat.*, xii., 1, 1901.

Adami¹ has collected 42 examples from the literature. They are often large, one recorded by Waldeyer being 63 pounds in weight.

Dermoids and teratomas are recorded; cysts are rare.

An important primary growth is the endothelioma, which occurs in the form of minute, flat, warty excrescences scattered over the serosa or as a thick sheet. It is due to an aberrant growth of the lining endothelial cells.

Matas² has recorded a curious case of primary myxosarcoma of the great omentum in which there was extensive secondary growth in the peritoneum, with a mucoid ascites.

Secondary malignant growths are common, and the omentum here is most liable to be affected.

The primary growth is usually a carcinoma found in the stomach, gall-bladder, pancreas, intestine, uterus, ovaries, and prostate. Multiple melanotic sarcomas sometimes are present, derived by metastasis from a choroidal melanotic sarcoma or a pigmented wart.

Abnormal Contents.—These are various. Besides the various exudates mentioned, the contents of the stomach and intestines, bile, urine, fecal masses, gall-stones, parasites—all may appear in the abdominal cavity. Free bodies are derived from a variety of sources, appendices epiploicæ which have become detached, subserous fibroids, ovaries, and mummified or calcified embryos.

¹ *Montreal Med. Jour.*, Jan., Feb., 1897.

² *Phila. Monthly Med. Jour.*, Dec., 1899.

THE RESPIRATORY TRACT.

THE NOSE.

Congenital Malformations.—Congenital absence of the nose and its cavities is observed only in the rare cases in which the skull and bony parts of the face show extreme variation from the normal. The individuals do not live. In cyclopic monsters the nose may be entirely absent or be represented by a small snout-like projection situated above the eye. A common abnormality is an extreme narrowing of the nostrils, absence of the septum and of the neighboring bony parts. In these cases the eyes are very close together. This deformity is described by Sömmering as *cebocephalia*.

Absence of the inferior turbinated bones has been observed by von Hyrtl. Congenital osseous closure of the posterior nares (choanæ) is a rare but repeatedly observed deformity.

The most common of the deformities consist in unusual obliquity of the nasal septum and its deflection toward one or the other side. Clefts in the *alæ nasi* and floor of the nose are also common.

Inflammations.—Inflammation of the nose, or rhinitis, is the most common diseased condition of the organ, and, indeed, one of the most frequent maladies of the human body. While in some cases the etiology of the affection is sufficiently apparent, the true cause of the ordinary forms is still in doubt, and it is a great question whether “overheating” and “getting the feet wet” are of any further significance than that they open avenues through which the real specific cause may enter.

Two chief forms of nonspecific rhinitis are described: acute and chronic.

Acute Catarrhal Rhinitis.—The most common and most simple variety of this form of the disease is the ordinary *coryza* or cold in the head. It is said to follow exposure to cold, seems in some cases to be the result of the absorption of abnormal digestive products (leukomains), and sometimes follows the inhalation of certain irritant substances, as powdered soap-bark and some of the irrespirable gases. Ordinarily the coryza is of very short duration, and after recovery leaves no structural or other alteration behind it. No sharp line, however, divides the ordinary “cold in the head” from the more continuous and severe forms, either as regards their duration or their anatomic alterations, so that from the ordinary simple coryza a step takes us to the persistent acute catarrhal rhinitis known as “rose cold” and “hay fever,” and the severe forms that sometimes occur in measles, scarlatina, variola, and traumatism. The most severe form of the acute catarrhal rhinitis is probably that due either to a primary diphtheritic infection or an extension of a pharyngeal diphtheria into the nose. As, however, the diphtheritic rhinitis has interesting peculiarities, it will be considered separately. The anatomic changes accompanying acute rhinitis are rather less marked than might be expected. The Schneiderian membrane is somewhat hyperemic, swollen, and tumefied. The mucous glands secrete actively, and pour

upon the membrane a large amount of serous or seromucous secretion. Microscopically this discharge is found to contain mucus, desquamated epithelial cells, few or many pus-corpuscles according to the severity of the inflammation, and a variety of bacteria—chiefly cocci—that have entered with the inspired air and been retained in the nose.

The stage of active secretion is usually preceded by a brief period in which, while the patient experiences considerable discomfort from the hyperemic and swollen condition of the mucous membrane, there is no secretion. The quantity of secretion diminishes gradually, and, by retaining dust and inspissating, forms crusts which adhere intimately to the surface of the nose. If these are forcibly removed, abrasions occur.

“Rose cold” and “hay fever” seem to have no anatomic alterations peculiar to themselves. They are characterized by repeated sudden paroxysms of hyperemia and secretion, supposed to bear some not yet proved relation to vegetable pollen, but more suggestive of a vasomotor neurosis of some kind.

Scarcely any limit can be placed upon the extent or severity of a rhinitis that would follow traumatism.

Many chronic cases of rhinitis develop from the acute, after passing through a subacute stage.

However, a large number of the chronic cases depend upon causes altogether different from those productive of the acute form, and are in consequence of a different nature.

Chronic catarrhal rhinitis sometimes results from congenital or acquired deformities of the nose with displacement of the bones. In other cases it may be brought about by polypi or other tumors, or may be part of tuberculous or syphilitic disease. It may also depend upon disease of the bones, retention of foreign bodies, and possibly upon the pressure of bacteria, of which large numbers are, very naturally, encountered in the secretions.

The anatomic changes are progressive, and permit of division into a *hypertrophic form or stage* and an *atrophic form or stage*.

Hypertrophic Rhinitis.—In this form the mucous membrane is hyperemic and hyperplastic, the veins are numerous and enlarged, the mucous glands enlarge and secrete a viscid mucus much more adhesive than that of acute rhinitis. The lymphatic tissue of the nose is apt to increase in amount and encroaches upon the air-passage. In many cases the inferior turbinated bones enlarge. It will at once be seen that almost all the prevailing conditions contribute to make the affection an obstructive one. Not infrequently it is impossible for the patient to breathe through the nose.

Atrophic Rhinitis.—This may begin as an atrophic disease or may succeed the hypertrophic form. As the name indicates, it is characterized by atrophy and disappearance first of the hyperplastic tissue of the early stage, then of the proper nasal tissues, including the bones. The nasal cavities are enlarged. The erectile tissue is replaced by newly formed connective tissue. The secretion changes in character, and becomes yellowish or greenish in color; retained in the nasal cavities the secretion may decompose and cause an extremely disgusting odor (*ozena*). Schuchardt found that the ciliated epithelium of the nose is lost and replaced by squamous cells. The secretion scabs and crusts, abrasions are common, but ulcers are rare.

Pseudomembranous or Diphtheritic Rhinitis.—Inflammations of the nose accompanied by the formation of a false membrane are rare. Accord-

ing to Potter, their frequency is about 2 per cent. of the cases of acute rhinitis. Birch-Hirschfeld asserts that they occur in inflammations of the nose depending upon scarlatina, erysipelas, and typhoid. Their relationship to diphtheria was suggested at an early date, but only since the development of the methods of bacteriology has it been possible to prove at least the majority of them to be cases of diphtheria. Of 10 cases studied by Park, all were diphtheria; of 10 more investigated by Ravenel, all were diphtheria. On the other hand, in a case worked up by Abel the pneumococcus was found, and in 3 cases reported by von Stock no Klebs-Löffler bacilli could be found.

The condition is not rare as an extension of pseudomembranous inflammation from the fauces and pharynx; but as a primary affection it is unusual and of interest especially from the hygienic point of view, for it seems quite possible for a mild case of diphtheritic rhinitis to spread contagion.

From the nose the disease may spread into the throat. Ordinarily the nasal diphtheria is unaccompanied by marked constitutional symptoms, and is inclined to run a mild though protracted course tending to recovery.

The anatomic alterations are those of severe acute rhinitis, with the addition of a whitish, firm, thick membrane which occludes the air-passages. Microscopically the membrane consists of fibrin with entangled epithelial cells and leukocytes. Culturally it is generally possible to secure the diphtheria bacillus. The bacillus found is the true diphtheria bacillus, as Abbott has shown, and is virulent; but in Ravenel's cases it was generally of feeble vitality, tending to die out when repeatedly transplanted from culture to culture. Ravenel explains the mild character of the disease and the rather slight danger of infection as dependent upon diminished vitality.

Tuberculous Rhinitis.—In spite of our well-supported theories concerning the primary infection of the human body with tubercle bacilli from the dust of the inspired air, the nose, upon which the deposition of the dust should be constant and in greatest amount, is rarely affected. Primary tuberculosis of the nose is unusual. It may be, however, that a more thorough examination of the nose than is at present carried on in practice may show us, especially in children, that it is often present when not expected.

The disease, as is usual, leads first to the formation of small tubercles with ordinary characters. Later, by the softening and excavation of these, ulcers with unlimited power of spreading and eroding are formed. The small ulcers may increase rapidly or slowly. From the mucous membrane the infiltration and ulceration lead to invasion of the cartilages and bones, with necrosis and at times perforation of the septum.

The tuberculous ulcers are most common in the lower part of the nose, upon the cartilaginous septum.

The occurrence of tuberculous lesions of the nose, like the occurrence of syphilitic lesions, is generally accompanied by ozena, brought about by the operation of the same causes. Tubercle bacilli in the discharges are by no means numerous.

Sometimes tuberculosis of the nose is not ulcerative or destructive, but hyperplastic, and polypi are formed, consisting chiefly of granulation-tissue containing tubercles.

Secondary invasion of the nose in advanced tuberculosis of the lungs is said not to be uncommon as a consequence of auto-infection.

Syphilitic Rhinitis.—The coryza, which is one of the common manifestations of syphilis, does not differ essentially from the ordinary coryzas, and therefore needs no separate description.

The special syphilitic lesions of the nose are of interest, though of rather rare occurrence. They consist of more or less severe, not infrequently progressive lesions, varying from a few papules to the most destructive erosions of the cartilages and bones.

The disease in its early manifestations usually shows a marked erythema, more likely to be in multiple local areas than general. Papules occur, and may break down and originate ulcers with a spreading tendency. No limit can be set to the extent of the disease. Necrosis of the cartilaginous and osseous tissues of the septum, with softening ("melting away") of this important structure, are common, and lead to the deformity known as "saddle nose."

When gummas form, they generally occur upon the septum, and are often the cause of subsequent perforations. The gummas originate either from the periosteum or perichondrium of the nose, and by their softening and ulceration produce widespread destructive lesions. The loss of tissue and subsequent cicatrization caused by a gummatous lesion are the most common causes of the "saddle-nose" deformity.

Such local lesions are usually associated with a general involvement of the mucous membrane, which is hyperemic, and the glands being enlarged there is a considerable amount of secretion. The degenerated and necrotic tissues form an excellent nidus for the growth of putrefactive bacteria, so that in syphilitic rhinitis ozena is very common. Cases with this condition are exceedingly unpleasant both to themselves and to others, the encrusting, foul-smelling nasal discharges being extremely offensive.

Glanders of the nose is very rare in the human being, and occurs in those exposed by their occupation to infection from diseased animals or their remains. The disease is characterized by circumscribed nodules or groups of nodules which rapidly soften and ulcerate. Neighboring ulcers frequently unite, forming larger ulcerated areas. The disease may extend to the deeper tissues, denude the osseous tissues, and bring about necrosis. In man the disease rarely remains confined to the nose, but generalizes itself, and leads to a fatal termination in a large number of cases.

As with other destructive processes of the nose, the disease is characterized by an altered secretion which has a purulent or purousanguinolent nature. In it the glanders bacilli may be found by the intraperitoneal inoculation of a male guinea-pig, which in a few days develops a suppurative orchitis, from the pus of which the glanders bacilli can be obtained in pure culture.

Lepa can also affect the nose. As, however, the leprous invasion of this organ is but a part of the disease, it is scarcely deserving of separate attention. It is characterized by the usual nodes and ulcers, and may extend into the frontal sinuses, and later, by perforation or extension through the skull, has been known to produce fatal meningitis.

Rhinoliths are concretions consisting chiefly of lime salts and dried secretions in laminated form. They are generally formed about foreign bodies and dried crusts from the nose. Their presence is accompanied by chronic rhinitis.

Tumors.—The greater number of the tumors of the nose are embraced

in the group known to surgeons as **polypi**. The term polyp, however, refers only to the outer form of the growth, signifying that it is circumscribed and more or less pedunculated, and not to the internal structure of the tumor.

The most common of the nasal tumors is that known as the *mucous polyp* or myxofibroma. It develops from the mucous membrane of the upper part of the nose, probably most frequently from the median aspect of the middle turbinated bone. The tumors are soft, gelatinous, translucent, and generally pedunculated. They are of various forms, and consist microscopically of delicate areolar tissue whose meshes enclose an albuminous serum containing a few round cells. In polyps of this kind no newly formed glandular alveoli are found. The surface is covered by a mucous membrane similar to that upon the surface from which the polyp grows. The interior of the polyp may contain cysts by myxomatous degeneration of the tissue.

The *adenomatous polyp* or adenofibroma differs from the above in that it consists in large part of newly formed glandular tissue, the alveoli with their beautiful columnar epithelium showing well in sections. The retention of secretion in these glands causes the formation of cysts, and thus increases the size of the tumor.

Occasionally the polypi are rich in blood-vessels, and may be described as *telangiectatic*. Ordinarily their blood-vessels are few.

The *nasopharyngeal polypoid* tumors grow from the periosteum and denser tissues, and extend into the cavity of the nose.

Sarcoma is of rare occurrence in the nose, except in cases of primary sarcoma of the antrum or neighboring parts. The rapid growth of tumors of this kind causes the nasal bones to become widely separated and much deformity of the parts to ensue. Should the sarcoma be primary in the nasal cavity, the reverse order occurs, and after rapid growth in the nose it extends to the antrum of Highmore later.

Carcinoma is also rare as an affection of the nose, though common as a disease of the skin contiguous to the nose. When external it is of the squamous type; when internal it is generally of the glandular type, having developed from the mucous glands.

THE LARYNX.

Congenital Malformations.—Total congenital absence of the larynx is one of the most unusual of the abnormalities, and seems only to occur in the extremely defective acardiac monsters. Congenital absence of parts is more common. Cases are on record in which the epiglottis and thyroid cartilages in part or in whole have been absent. Congenital fistulæ, abnormally large or small size of the parts, and an unusual segmentation of the cartilages seem to be rather common, all the abnormalities being more common in connection with the epiglottis than other parts.

The rare cases of dilated Morgagni's sinuses are pointed out by Birch-Hirschfeld as of interest because of the occurrence of such conditions normally in certain of the apes.

Sometimes there are adventitious cartilages or a number of fragments representing what should be single cartilages.

The scope of this section does not permit of consideration of the various paralytic effects of section or disease of the motor nerves of the larynx.

These find their proper place in text-books devoted exclusively to the diseases and anomalies of the larynx.

Inflammations.—Inflammation of the lining membrane of the larynx is a very common malady. It occurs in consequence of exposure to cold, violent strain of the voice, traumatism, and the inhalation of irritating vapors.

Of *acute forms*, such as would result from the causes given, the pathologic alterations are slight and more readily recognized during the life of the patient, by a laryngoscopic examination, than after death.

The mucous membrane of the larynx may be universally hyperemic, or, as is more common, certain parts of it, as the vocal cords or epiglottis, may be red and hyperemic. The epithelium is partially desquamated, and there is an increased amount of mucous or mucopurulent secretion. This is the extent of the alterations in ordinary cases, which, because of the mild character of the changes, readily recover.

If the case be unusually severe and protracted, ulcerations may form upon the vocal cords and at their posterior commissure, and the mucous membrane becomes infiltrated with leukocytes and thicker than normal.

Occasionally, as the result of violent trauma, a serous infiltration of the inferior surface of the epiglottis and aryteno-epiglottic folds, extending to the neighboring mucous membrane, and even to the vocal cords, may occur—*acute edema of the glottis*—and by distorting and closing the air-passages produce death.

A word of caution must be given at this point lest the acute edema be confounded with the chronic edema of the glottis that occurs in venous congestion from cardiac failure, pulmonary emphysema, compression of the veins of the neck, etc. The chronic edema, forming slowly, is a symmetric condition, as a rule; while the acute edema, depending upon the irregular nature of the traumatism, is quite often unilateral. Acute edema of the glottis may also follow the extensive and often destructive processes of carcinoma, syphilis, tuberculosis, and diphtheria.

After death the fluid in edema of the glottis may ooze out, thus diminishing the swelling, but the aryteno-epiglottic folds are then thrown into wrinkles and folds.

In violent acute inflammations—croupous, diphtheritic, gangrenous—and sometimes in syphilis and tuberculosis, the invasion of this submucous tissue by bacteria causes a *phlegmonous laryngitis*, with abscess formation in the mucous and submucous tissue. These abscesses may rupture externally into the neck, or internally into the larynx or pharynx.

The extension of the phlegmonous processes to the deeper tissues causes perichondritis in most cases. This may be severe and lead to the exfoliation of entire smaller cartilages, like the arytenoid.

Serious suppurative inflammations of the larynx may also result from the extension of inflammation from the pharynx, tonsil, etc. They are also not unusual in the course of typhoid fever, scarlatina, and pyemia.

When the cause of acute laryngitis is not readily removed, a *subacute inflammation* results, and permanent anatomic changes may occur. Thus, the vessels become dilated, the epithelial desquamation is irregular and patchy from the occurrence of regenerating areas in the midst of denuded surfaces. Round-cell infiltration of the mucous membrane occurs. The mucous glands become enlarged, and upon the under side of the epiglottis, the false vocal cords, and in Morgagni's sinuses a peculiar granular appearance—*granular*

laryngitis—occurs. This form might be regarded by some as a chronic form of the disease. No fixed boundary separates the acute and the chronic forms of *laryngitis*.

Chronic laryngitis sometimes follows repeated attacks of the acute. It is most common in those whose vocations require constant use or more or less abuse of the voice. It is therefore to be expected among criers, auctioneers, singers, lecturers, political speakers, etc.

The chief anatomic changes consist in dilatation of the vessels of the larynx, atrophy or hyperplasia of the mucous membrane in all its layers and elements, and a "qualitatively or quantitatively altered secretion." The mucous membrane is irregular, uneven, and granular. Erosions of the membrane are common, but deep ulcerations are always suggestive of tuberculosis and syphilis.

According to the particular character and position of the anatomic changes, different observers have used descriptive names. Thus, the already mentioned venous dilatation has been described by Sir Morel Mackenzie as *phlebectasia laryngea*; an uneven, coarsely granular appearance of the vocal cords as *chorditis tuberosa* by Türk; and a very common thickening of the mucous membrane of the vocal cords and side walls of the larynx, which becomes whitish gray in color, dense, and hard, as the *pachydermia diffusa laryngis* of Virchow.

Sometimes in chronic *laryngitis* the columnar epithelium of the larynx entirely disappears, to be replaced by squamous epithelium.

A very common alteration of the epithelium takes place upon the vocal cords of singers and others, and seems to represent an early stage of the *pachydermia laryngis* above mentioned. It consists of a bluish-white or grayish-white thickening of the superficial layer of epithelium at the posterior upper surface of the vocal cords, near the commissure. This thickening consists of a superficial pellicle, and can be removed with the forceps. When removed, the surface remaining is not abraded, but consists of squamous epithelium from which the superficial layers have been torn off.

When the thickening described as *pachydermia laryngis* is widespread, it is a well-characterized affection, and has been looked upon by some (Orth) as akin to the tumors.

Diphtheria.—This is an acute infectious toxic disease, characterized by the occurrence of local, superficial, fibrinous inflammations, most common in the pharynx, but also occurring in the larynx, nose, ear, conjunctiva, genitalia, and, though rarely, upon wounds. Diphtheria of the larynx may be primary, but usually occurs secondarily to diphtheria of the pharynx by extension. Whether primary or secondary in the larynx, it manifests itself by the occurrence of a tough yellowish pseudomembrane, either disposed in flakes upon the mucous membrane or forming a tubular mould of the organ. The vocal cords are peculiarly subject to the membranous formation. When attached to the epiglottis, the false membrane is generally found on the under side and upon the aryteno-epiglottic folds. The exudate may fill up Morgagni's folds. It may also extend down into the trachea as far as the bifurcation and into the bronchi.

Microscopically the false membrane consists of fibrin-threads, forming a dense mass or net in whose meshes leukocytes are numerous. The proper methods of staining will also reveal very numerous diphtheria bacilli in the membrane.

The membrane is sometimes intimately adherent to the mucous membrane beneath, especially upon the vocal cords and other structures covered with squamous epithelium. Sometimes, on the other hand, its attachment is loose. This is especially true of the later stages of the disease and in cases treated with antitoxin, when the whole pseudomembrane may suddenly detach and be expectorated.

When the attachments are firm and the membrane is artificially divulsed the epithelial cells come with it, and an abraded surface remains, upon which, during the course of the disease, another fibrinous layer soon forms.

The pseudomembrane is not always typical in appearance, but is subject to variations of color, being sometimes nearly white, sometimes yellowish. The consistence is not always the same. It is sometimes so tough as to be divulsed with difficulty, at other times so friable that it seems to be rather a granular deposit than a membrane.

Nondiphtheritic membranous laryngitis, almost exactly like the true diphtheritic laryngitis, is not uncommon. The distinction between it and diphtheria cannot be made clinically. In the one case the disease depends upon the Klebs-Löffler bacillus; in the other upon the growth of streptococci or upon the inspiration of violently irritating substances, such as steam, chlorin gas, acetic acid, ammonia, etc. Rarely cases have been met with in which unusual bacteria, such as the colon bacillus and pneumococcus, produced membranous laryngitis.

Certain of the specific diseases, such as variola, measles, and scarlatina, are occasionally accompanied by a membranous laryngitis.

Typhoid Fever.—That interesting lesions of the larynx occur in typhoid fever seems to have been first pointed out by Eppinger, who discovered that at the base of the epiglottis, on the false vocal cords, and on the anterior commissure diffuse, soft, elevated, nodular areas occurred, in which the mucous membrane and subjacent tissues were infiltrated with round cells. Eppinger expressed the opinion that the lesions of the laryngeal and intestinal mucous membranes were identical. No proof of the correctness of this view has yet been brought forward. The facts that the condition occurs in typhoid fever, that the infiltrated areas frequently ulcerate, and that their recovery is protracted, are, however, very suggestive, and Eppinger may have been right in his assumption.

In addition to the lesion described, the larynx in typhoid fever is very commonly subject to catarrhal inflammation.

Variola.—Very often in variola the mucous membrane of the larynx, when inspected, is found to present small punctiform lesions which might well be mistaken for modified pustules. They are not such, however, but consist of small areas of submucous infiltration of round cells, and superficial collections of desquamating epithelium.

The lesions do not run a course at all similar to the pustule.

In severe cases of variola membranous laryngitis may occur.

Tuberculous Laryngitis.—Tuberculosis of the larynx occurs both as a primary and as a secondary affection, but it is most frequently secondary to tuberculosis of the lung. The reason for this is quite apparent when one remembers that all the infectious discharges of the lung pass through the larynx before expectoration.

The disease begins with the formation of a few miliary tubercles, generally situated upon the edges and under surface of the epiglottis, and upon

the vocal cords, near the posterior commissure. The tubercles occupy the mucous or submucous tissue, and according to Birch-Hirschfeld are always above the mucous gland layer. The tubercles increase in size pretty rapidly, caseate, and form ulcers which gradually increase in size, the extension being often favored by secondary nasal infection.

Sometimes, instead of caseation and ulceration, the tuberculous inflammation takes on a hyperplastic development with excrescences rich in typical tubercles. In these cases, however, as in the others, the hyperplastic tissue sooner or later breaks down and leaves irregular, excavated ulcers with infiltrated borders. From the large ulcers tuberculosis spreads by the formation of new tubercles.

The tubercles as they spread may invade the mucous, submucous, and perichondrial tissues. In the latter considerable caseous deposits sometimes occur.

Although common upon the epiglottis and vocal cords, as mentioned, the disease is not limited to these parts, as it often affects the anterior and posterior walls of the larynx.

The occurrence, course, etc., of tuberculous laryngitis are not regular. Sometimes the lesions ulcerate early, sometimes not until quite large projecting hyperplastic masses have formed. The ulcerations are rather more apt to occur rapidly upon the vocal cords than elsewhere, probably because of the avascularity of those parts.

As would be expected, tuberculous disease of the larynx does not occur without an accompanying catarrhal laryngitis. On account of the tissue destruction, unexpected accidents, such as edema of the glottis and phlegmonous laryngitis, may occur.

No limit can be placed upon the extent of the disease. The whole interior of the organ may be converted into an uneven, nodular, ulcerated, almost unrecognizable tissue; by perichondritic invasions necrosis and exfoliation of whole cartilages may occur.

In rather rare cases tuberculous disease of the larynx assumes a tumor-like form. This occurs not simply as papillary excrescences at the edges of the ulcers, but as distinct, circumscribed, projecting, solitary or multiple, rounded, smooth bodies, varying in size from a pea to a hazelnut. Histologically they consist of dense granulation-tissue, well on toward connective-tissue formation, containing closely approximated tubercles. Such forms have been described by Schintzler, John, Mackenzie, Ariza, Percy Kidd, and others.

Tuberculosis (lupus) of the nose and pharynx may extend into the larynx and show itself by the eruption of millet-seed- or hemp-seed-sized nodules, more or less isolated, prominent, and papillary. Sometimes these nodules may be aggregated in clusters. The outcome of the disease is the formation of unevenly nodulated prominent masses, and, later, ulceration may form. One characteristic of the form of tuberculosis commonly called lupus is the abundant formation of scar-tissue, which, by its contraction, brings about deformities.

Syphilitic Laryngitis.—Laryngitis is a very common symptom of syphilis, and occurs in a variety of forms, sometimes mild, sometimes serious.

The mildest form is that of a *simple catarrh*, in which the mucous membrane is hyperemic, rose red, livid, or brownish in color. Upon the vocal cords a dirty-grayish discoloration is sometimes observed. Small and some-

times large erosions of the mucous membrane occur. Here and there, especially upon the vocal cords, there may be epithelial thickenings.

The *inflammatory infiltration* which has been described in syphilis consists of a subepithelial infiltration of round cells, generally upon the vocal cords, epiglottis, and posterior laryngeal wall. They form homogeneous thickenings, with some deformity of the parts.

Mucous patches are rare, but sometimes occur in the larynx. They are generally observed upon the free edges of the epiglottis, over the cartilages of Santorini, on the arytenoid cartilage, or in the aryteno-epiglottic fold. According to Lewin, they occur in the middle of the vocal cords.

The patches vary in shape, sometimes being round, sometimes elongated. They project slightly, and are grayish white in color, with reddened borders. When the thickened epithelial coverings desquamate the patches become very red.

Ulcerations of the laryngeal tissues probably form the most common syphilitic lesion of the larynx. They are sometimes superficial, sometimes deep. Their borders are usually greatly elevated and thickened, and their surfaces covered with a grayish deposit with a subjacent whitish infiltration. The ulcerations may occur from erosions following the catarrhal laryngitis and inflammatory infiltrations; they may follow the mucous patch, and may result also from destruction of tissue caused by a gumma.

The ulcers are generally situated upon the epiglottis, vocal cords, or posterior wall of the larynx. The shape of the ulcer varies somewhat with its cause. The ulcers following the inflammatory infiltration are apt to be very irregular in size and outline, and have ragged, infiltrated bodies with papillary projections. Ulcers resulting from gummas are sharply circumscribed, deeply excavated, and generally smaller. The former ulcers are as a class more superficial than the latter. When deep they, of course, affect the cartilages and bring about necrosis and perichondritis.

Perichondritis may, however, also follow deep ulcerations originating in inflammatory infiltrations. When the ulcerations are deep and cause necrosis and perichondritis, it is not uncommon for exfoliation of fragments of cartilage to occur.

Recovery of laryngeal syphilis may begin at almost any part of the process. Regenerative changes are always accompanied by massive prolifera-



FIG. 269.—Tuberculous ulceration of the larynx (drawn from a specimen furnished by Dr. Frederick A. Packard).

tion of connective tissue, so that a large cicatrix, generally of more or less stellate appearance, occurs. When such a cicatrix is small, of course little, if any, disadvantage is noticed; but when the ulcerations have been extensive the result of the contraction of the cicatrices is such as to deform the organ. Ziegler points out that neighboring parts of the organ, denuded of their epithelium, may, in the course of recovery, grow together and further aid in the resulting deformity.

The irregular contraction of bands of fibrous tissue encircling areas of healthy mucous membrane causes these to project considerably, and thus originate the conditions that favor the development of papillomas, which later may become sufficiently large to obstruct the air-passages.

The *gummas* of the larynx seem to have no selective tendency, but occur in any part of the laryngeal structure that is well provided with circulation. They may be single or multiple. When single they may be much larger than when multiple, and sometimes occur as large circumscribed nodes with smooth surfaces. Originally dark red, they later become yellow in color. The single gumma may also be rather diffuse, especially when connected with inflammatory infiltrations.

When multiple they are observed as more or less numerous round bodies, varying in size from that of a shot to that of a pea, sharply circumscribed, as a rule, and projecting from the surface of the mucous membrane. Sometimes they will be so closely approximated as to give the impression that they would coalesce. Such a patch of gummas has been described by Lewin as the "small nodular syphilid."

Lepra may affect the larynx in the course of its generalizations. It does not occur primarily in the organ. The anatomic alterations consist in the formation of nodules resembling the syphilitic papules or follicular buboes. The surrounding mucous membrane is reddened, swollen, and projects beyond the node. There may be so many nodules present as to suggest a single infiltration where they are massed together. The affected parts of the organ become remarkably thickened, stiff, immovable, and superficially rough. As with the other granulomas, the lepra-nodules of the mucous membrane have a pronounced tendency to ulcerate. The ulcers may cicatrize, and, like the syphilitic scars, the resulting contracting connective tissue not rarely leads to deformity and stenosis. Gottstein says the resulting deformity may be so great as to reduce the interior of the larynx to the size of a lead-pencil.

Glanders may affect the larynx in cases in which it invades the air-passages. The lesions follow the type normal to the disease, and consist of subepithelial cellular nodes, which undergo necrosis, ulcerate, and form the starting point of larger or smaller denuded suppurating surfaces.

Tumors of the Larynx.—The larynx is frequently occupied by neoplasms, both benign and malignant. Of 1100 cases studied by Bruns, 602 were papillomas, 346 fibromas, 73 mucous polypi, and 27 cysts. From these figures it is clear that the **papilloma** is the most common tumor of the larynx. The tumor bears a distinct resemblance to the hard papilloma of the skin, and may attain a considerable size. It is usually of inflammatory origin in the beginning, and is generally seated upon the vocal cords, to which it is attached either by a broad or a long pedicle. The tumor may consist of a simple wart or may be dendritic, in which case it is likely to be large and to cover a considerable extent of the laryngeal mucous membrane.

Papillomas may be single or multiple. Originating from the tissues of the vocal cord, the tumor is usually covered with squamous epithelium, though if its point of origin be elsewhere it may be covered with cylindric epithelium.

The idiopathic papillomas generally occur in young people; the inflammatory form occurs in those that have previously suffered from tuberculous, syphilitic, or other ulcers.

According to Sutton, the tumor may originate upon or beneath the vocal cord, and not uncommonly immediately beneath the attachment of the vocal cords and thyroid cartilage. Exceptionally a large mulberry-like wart has been seen growing from the floor of the sinus pyriformis.

The variation in size is great—from that of a pin-head to that of a cherry. They are generally small, varying from a hemp seed to a pea in size. When pedunculated and mobile they dangle in the larynx between the vocal cords, where they sometimes are retained with unpleasant and dangerous results. The tumors are sometimes, especially in children, subject to spontaneous cure. They appear pink or red, according to the amount of blood they contain.

Fibroma of the larynx is also a common tumor. It is usually pedunculated, about the size of a lentil, though sometimes as large as a hazelnut. The usual point of occurrence is upon the vocal cord. The tumors are at times vascular.

Adenoma or polyp—mucous polyp—of the larynx is by no means rare. These tumors usually occur upon the vocal cords, and may have their beginning in the ragged borders of ulcers. The chief characteristic is the soft consistence and mucoid or colloid appearance. They are generally about the size of a pea, rounded and smooth, but may be lobed. Upon section they diminish markedly in size from the escape of mucus from the small cysts that they contain. Microscopically they are made up of areolar tissue, an epithelial investment, and a number of the glands belonging to the membrane. The glands (mucous glands) are all in a condition of cystic retention and consequent cellular degeneration. Polypi are, of course, benign growths.

Among the rare benign tumors of the larynx the literature reveals cases of lipoma, myxoma, chondroma, solid adenoma, and cavernous angioma.

The lipoma has the ordinary structure. A rare case is that reported by Holt, in which a lipoma growing from the aryteno-epiglottic fold and side of the epiglottis extended into the esophagus for 22.5 cm. (9 inches).

Retention cysts of the mucous glands of the larynx may occur upon the sides of the epiglottis and in Morgagni's pockets.

Malignant Tumors of the Larynx.—*Sarcoma* of the larynx is much less frequent than carcinoma. Mackenzie collected 9 cases of spindle-cell sarcoma. They generally spring from the tissues of the epiglottis, but may occur upon the vocal cords. Sometimes the sarcomas resemble the pedunculated fibromas referred to, but are softer. Their color is dark red or meat red, sometimes yellowish. The surface is sometimes smooth, sometimes warty. Round-cell sarcomas and fibrosarcomas also occur; lymphosarcoma of the mucous membrane has been described.

Carcinoma of the larynx is a rare primary affection. The tumors are divided by Sutton into *intrinsic* forms, which arise from the mucous membrane of the vocal cords, ventricles, and ventricular bands; and the *extrinsic*

forms, arising from the aryteno-epiglottic folds or mucous membrane covering the arytenoids and interarytenoid folds.

In the intrinsic forms the tumor usually begins in one of the ventricles, and is almost invariably warty and rich in cell-nests. The papillomatous appearance of this tumor is important to bear in mind when making a diagnosis between it and papilloma. However, as Sutton remarks, the wart is a disease of early life; carcinoma of adult life. The tumors are rapid in progress, and life is rarely prolonged beyond two years from the time they are first observed.

The extrinsic form is much more malignant, and invades lymphatic glands at an early period.

The intrinsic forms are apt to degenerate and produce ulcerations with ill-defined borders and a marked tendency to spread.

Phlegmonous laryngitis and edema of the glottis may result from the infection and destruction caused by the ulcers.

Carcinoma growing from the glands of the larynx is a very rare and very malignant affection. Clinically the tumors can be divided into those that are hard and those that are soft. Pathologically the tumors do not differ particularly from those of other organs.

Secondary carcinoma is much more frequent than the primary form, generally originating in the thyroid, pharynx, or esophagus. Death from carcinoma of the larynx is generally due either to inspiration pneumonia from the inhalation of infectious materials from the tumor and its necrotic portions, or from a stenosis of the esophagus caused by the backward extension of the disease.

Diseases of the Cartilages of the Larynx.—These are practically all secondary to the various ulcerative affections already described. Occasionally, however, erosion of the cartilages is caused by external pressure, as in aneurysms, or by the pressure of the larynx itself upon the neighboring tissues when marantic individuals are obliged to lie for long periods in bed. Such cases generally show necrosis of the posterior part of the cricoid cartilage from pressure upon the vertebral column.

Perichondritic abscesses may rupture into the larynx and produce a dangerous and septic inspiration (broncho-) pneumonia.

As a rule, the acute inflammatory affections of the cartilages are not so serious as those coming on in the course of tuberculosis, syphilis, and carcinoma. The acute inflammations form abscesses which evacuate and recover. Syphilis also recovers with deforming cicatricial formations. Tuberculosis and carcinoma are progressive lesions, rarely healing properly, and apt not only to disorganize the cartilages, but also to bring about general involvement by the disease disseminating itself through the lymphatics and blood-vessels.

THE TRACHEA.

Congenital Malformations.—Congenital deformities of the trachea are not at all common, especially if such deformities are considered independently of the larynx and lungs. In acephalic monsters the trachea may be entirely absent, sometimes the larynx and lungs being present, sometimes not. Occasionally the trachea divides so high up that the larynx passes almost immediately into the bronchi. Sometimes there is atresia of the trachea, the tube ending blindly or in a very narrow bronchus. Sometimes,

in consequence of incomplete separation of respiratory and digestive tubes, a communication exists between the trachea and the esophagus, near the tracheal bifurcation. These malformations are incompatible with the life of the individual.

Absence of tracheal rings, fusion of the rings, longitudinal or transverse cleavage of the rings, are more or less common, but without considerable importance. Also unimportant, but of occurrence, are abnormally long or short, narrow or wide, or septate tracheæ. Rarely, but occasionally, the trachea divides into three instead of the normal two bronchi, the extra bronchus generally being upon the right side. Congenital diverticula of the trachea also occur.

A not infrequent malformation is a fistula of the trachea occurring in consequence of failure of the embryonal union of the third and fourth visceral arches, and appearing generally in after-life as a minute opening or small cyst, situated upon the right side of the neck, at the inner border of the sternomastoid muscle, about an inch above the sternoclavicular articulation, sometimes a trifle higher up. The opening, as seen externally, is only sufficient to admit a bristle.

Inflammations.—Inflammations of the trachea occur, though with mild severity, in the majority of cases of bronchitis and laryngitis. It is also infected by tubercle bacilli in tuberculosis of the lungs, bears its share of the local manifestations of such exanthemas as measles, variola, etc., and is affected like other respiratory organs in influenza, whooping cough, etc. Primary inflammation of the trachea except as a result of traumatism is rare. The anatomic alterations are slight, consisting in hyperemia, some tumefaction of the mucous membrane, and hypersecretion by the mucous glands. The disease generally passes away without permanent alterations.

Tuberculosis.—Primary tuberculosis is rare. Secondary tuberculosis from infectious material from the lungs produces subepithelial tubercles that do not attain a large size, but frequently soften, ulcerate, and expose the cartilages, bringing about local necrosis.

Syphilis.—Gumma may form in the trachea, and by softening and evacuation produce rounded or irregular excavated ulcerations, followed by stellate or irregular scars, sometimes constricting the tube. Most syphilitic inflammations of the trachea are extremes of ulcerative laryngitis.

Tumors of the trachea are rare. Ziegler mentions fibroma, sarcoma, chondroma, osteoma, adenoma, and carcinoma. Any metastatic tumor may occur secondarily in the trachea. Many of the secondary tumors have their primary seat in the thyroid gland. Primary carcinoma of the trachea may grow from the mucous glands. The mucous glands may also become cystic and attain the size of a hazelnut or walnut. They generally occur in the posterior wall, and extend externally between the trachea and esophagus. Secondary carcinoma of the trachea from primary disease of the esophagus is also common.

THE BRONCHI.

Bronchitis, or inflammation of the larger bronchial vessels, is one of the most common diseases. It is generally an acute malady of a catarrhal nature. It is characterized by hyperemia and slight swelling of the mucous membrane, by mucous degeneration of the epithelial cells of the mucous membrane and their desquamation, and by hypersecretion of the mucous

glands. In the ordinary mild forms the inflammatory exudate is mucous or serous; it may, however, be distinctly purulent, or may be fibrinous in rare cases. When the disease is chronic and the secretions are retained and putrefy from bacterial invasion, the exudate may be putrid or fetid.

In addition to the mild anatomic changes described, there is in most cases an infiltration of the mucous membrane, and sometimes of the sub-mucous tissues, with round cells. This is especially characteristic of the purulent form. The exact extent of the cellular infiltration must bear a distinct relation to the severity of the inflammation. It may involve all the coats of the air-tubes and encroach considerably upon the surrounding pulmonary tissue, forming a peribronchitis.

The desquamation of epithelium may leave considerable-sized areas of membrane denuded. The expectoration contains these cells and the numerous goblet-cells.

The disease may be primary, occurring either from an infection the nature of which is unknown; or, like coryza, it may occur from some unknown intoxication associated with or dependent upon disturbances of nutrition.

Bronchitis may also be caused by the inhalation of infectious materials from higher parts of the respiratory tract or by irritating substances in the air, or from the circulation of irritating substances through the blood sent to the lungs, and from foreign bodies.

When the causes are such as persist for considerable time the disease may become chronic, and then it may be associated with ulcerations, atrophies, and hyperplastic growths following the healing of the ulcerated areas.

The ordinary acute forms generally recover without sequelæ. The epithelium regenerates by karyokinesis, the secretions are expectorated, the cellular infiltrations are absorbed, and the membrane appears normal.

The chronic cases may cause atrophy of the coats of the vessels or erosions, and thus tend to diminish the resisting power of the vessel to the pressure of the entering air. The result of this is dilatation of the tubes—*bronchiectasis*. Ordinarily two factors, a diseased tubular wall and the pressure of the air, combine to produce them. A case of congenital bronchiectasis has been reported by Grawitz.

Bronchiectases are sometimes cylindric, sometimes fusiform, more rarely saccular. The cylindric and fusiform forms may be common to a number of tubes, a whole bronchial branch suffering; while the saccular form causes single or multiple local enlargements of varying size. Sometimes both forms occur simultaneously. The saccular multiple form may extend along a bronchus, like a string of beads.

As would be expected from the conditions of their formation, the walls of bronchial dilatations are usually infiltrated with round cells, the cartilages not rarely disappear, the epithelium is desquamated, and the cylindric epithelium of the mucous membrane may be replaced by cuboid or squamous epithelium without cilia. Ziegler and others explain heightened air-pressure as conducive of dilatation by showing that when one bronchus or one of the smaller tubes is obstructed, inspiration throws an additional amount of air into the unobstructed portions, some of which may not be able to bear it.

Another possible cause of bronchiectasis is the shrinkage of pulmonary tissue around a bronchus, which then is stretched into dilatation.

Pulmonary cysts occurring in indurated lungs with bronchial dilatations

may be nothing more than bronchiectatic cavities filled with secretion. An indurated lung may be full of such cavities or cysts.

Chronic bronchitis sometimes produces hyperplasia instead of atrophy of the wall of the bronchi, especially where plugs of partially inspissated secretion are retained. Sometimes, without apparent cause, the thickening occurs in tubes whose lumen is unobstructed, and extends along the tubes for a considerable part of their distribution. The proliferative inflammations of the bronchial tubes may be divided into *endobronchitis*, *mesobronchitis*, *peribronchitis*, and *peribronchial lymphangitis*.

Peribronchitis originating from within is with some difficulty differentiated from that of pleurogenic origin, in which bands of connective tissue forming in consequence of chronic hyperplastic pleuritis extend inward along the lobar septa and bronchial areas.

Inflammations of the bronchioles are nearly always associated with pulmonary changes, and are discussed in connection with pulmonary processes.

Croupous bronchitis associated with the formation of a pseudomembrane is generally of diphtheritic nature, and results from the inhalation of infectious matter from pharyngeal or laryngeal diphtheria. It also occurs in croupous pneumonia, in which disease the bronchial vessels are all filled with fibrinous material similar to that expectorated.

While in croupous pneumonia the air-tubes are liable to be full of fibrinous semisolid matter, in diphtheria they are lined by a whitish pseudomembrane.

Fibrinous Bronchitis.—This rare disease is a chronic affection of the bronchial tubes, characterized by the occasional expectoration of firm dendritic fibrinous casts of the finer portions of the bronchial tree. The material composing the mould resembles fibrin, but has been regarded by Neelson as an inspissated mucus. It does not always respond to the fibrin-tests. Two cases of genuine fibrinous bronchitis have been described by Herzog.¹ The plugs are rich in Charcot-Leyden crystals, and also frequently have Curschmann's spirals attached to them, generally at the finest branchings.

According to Birch-Hirschfeld, there seem to be two varieties of the disease—one, acute, beginning with catarrhal bronchitis, sometimes with sudden marked dyspnea, fever, and then in the course of a few days the expectoration of characteristic fragments. The chronic form develops, as a rule, at the close of catarrhal bronchitis, and also occurs as a complication of pulmonary tuberculosis.

The larger portions of the expectorated moulds are generally tubular, but the finer portions are solid, so that no air of any account could have entered the diseased area.

Tuberculous bronchitis is an almost invariable accompaniment of pulmonary tuberculosis. Beginning in the bronchioles, it extends to the larger tubes, and may be widespread in the bronchial tissue. It begins with the ordinary gray tubercles, progresses with the softening and discharge of their contents, and terminates by the formation of excavated ulcers. The entire bronchial wall, in the smaller bronchi, often succumbs to the necrosis following the tuberculous inflammation. Tuberculosis of the larger tubes is a fruitful source of ulceration and perforation of the tubes. With the perforation of the tubes their contents, whether tuberculous, putrid, or septic, begin to infiltrate the pulmonary tissue in the immediate neighborhood, with

¹ *Centraltbl. f. allg. path. u. path. Anat.*, viii., 1008, 1897.

consequent abscess, necrosis, caseation, or simple peribronchial inflammation. Bronchiectasis may result from destruction of peribronchial tissue, the dilatation having roughened and ulcerated walls. Sometimes what seems to be a bronchial dilatation is in reality an ulcerated cavity in which the bronchus ends at one side and begins again at the other, no remnant of a wall being left. This cavity contains tissue-remnants, both pulmonary and bronchial, and its walls may be cheesy, suppurating, or solid according to its origin. Its contents are generally invaded by putrefactive bacteria. Leucin, tyrosin, and other crystals may be found. If the cavity be tuberculous or gangrenous, it is likely to continue to increase in size. If, on the other hand, its genesis is the result of transitory conditions, reactive inflammation may occur about the diseased tissue, and it will diminish very much in size by cicatricial contraction and develops a comparatively smooth and healthy-looking lining.

Syphilitic ulcerations occasionally, though rarely, occur in the

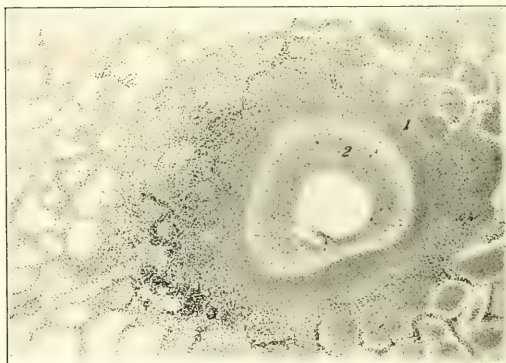


FIG. 270.—Caseous bronchitis; transverse section through a small bronchus and surrounding lung-tissue. The wall of the bronchus is completely broken down, caseated (1), its lumen is partly filled with the cheesy material (2). The tuberculous process extends in a circular manner outward to the surrounding lung-tissue; the alveoli of the latter are infiltrated and filled with numerous confluent tubercles (3). $\times 49$. (Dürk).

bronchi. Like the tuberculous ulcers, they may lead to perforation and its numerous sequelæ.

Tumors of the bronchi are rare. Occasional polypoid outgrowths from the membrane are met in catarrh. Small fibromas and lipomas are on record. Birch-Hirschfeld has reported 3 cases of primary sarcoma of the bronchi, all of the small round-cell variety.

Primary carcinoma of the bronchi is rare, but can occur from the mucous glands of the larger tubes, and according to Birch-Hirschfeld remains localized to one lobe of a lung, generally a lower lobe.

Bronchial calculi occasionally occur from the calcareous infiltration of retained material—inspissated inflammatory deposits, etc., and from incrustation of accidentally inspired foreign bodies. The latter variety is rare, however, because the foreign bodies generally cause purulent inflammations.

THE LUNGS.

Congenital Malformations.—The congenital malformations of the lungs are few in number. In acephalic monsters the lungs may be entirely absent. Congenital absence of one lung, either the right or left, is more common. In such cases the remaining lung is the seat of compensatory hypertrophy and inflation. According to Birch-Hirschfeld, hydrothorax may be present in that side of the thorax whose lung is lacking. The bronchus of the absent lung may be absent or may terminate blindly.

Occasionally abnormalities in the arrangement and number of the lobes of the lungs present themselves. They are, however, of no particular importance.

The most common abnormalities are those which have to do with the postnatal expansion of the organ in inspiration. Atelectasis of both or one lung may occur, or atelectasis may occur in local patches, the remainder of the lung showing a condition of compensatory distention.

Atelectasis.—Atelectasis, or collapse of the lung, may depend upon failure of the lung to expand at birth, or upon conditions subsequently arising by which collapse is brought about.

Congenital atelectasis or pneumatosis is a condition in which, in spite of respiratory efforts made by the child after birth, the lungs fail to inflate. The condition is usually caused by the inspiration of mucus, etc., by which the bronchial tubes are obstructed and the air excluded. It may also result from pressure upon the lung, and insufficient respiratory energy, especially in premature infants.

The condition is in reality the persistence of the fetal type of the pulmonary tissue. After death and the removal of the lung it may be artificially inflated and made to assume the ordinary appearance.

Acquired atelectatic conditions are more frequent and usually less extensive than the congenital form.

Obstructive Atelectasis.—This form of the disease depends upon the obstruction of the bronchi and the absorption of the air behind the obstruction. The bronchial obstructions may depend upon a variety of causes, as occlusion by tubercular growths, constriction by cicatricial bands, tenacious secretion, swelling of the mucous membrane, etc. The absorption of the air, according to Lichtheim, is a tedious matter. The oxygen is first taken up, the carbon dioxid later, and the nitrogen last. When the gas is completely absorbed the lung returns to its fetal condition.

The capillaries are pale red; the lung is dark red or brown red in color, solid and nonrepitant; it sinks readily in water. The surface of a lung the subject of obstructive atelectasis appears to the eye to be mottled and nodular from the alternating normal and atelectatic areas.

Compression atelectasis is seen in cases of compression of the lung by serum or pus within the pleural cavity, morbid growths, etc. In rare cases upward displacement of the diaphragm, kyphotic or scoliotic deformities of the spine may also press upon the lung.

Marasmatic atelectasis, according to Eichhorst, is occasionally seen in diseases such as tuberculosis, typhoid fever, etc., and is said to depend upon the continued maintenance of one position.

When atelectasis persists for some time, it becomes impossible again to inflate the lung, especially when inflammation occurs simultaneously with or

follows the atelectasis. Not rarely in atelectatic lungs small hemorrhages occur, and are followed by pigmentation. Atrophy by fatty metamorphosis of the alveolar epithelial cells occurs sooner or later, after which the alveolar septa being in apposition unite, hyperplasia of the connective tissue takes place, and gradually the atelectatic area is transformed into a pigmented mass of connective tissue.

Atelectatic areas that have occurred in infancy and remained to adult life usually appear as depressions upon the pleural surfaces. They are generally covered with thickened pleura, and are entirely free from the coal-dust seen elsewhere in the lung. The costal pleura with which the atelectatic area comes in contact is also frequently thickened. When incised, numerous bronchiectases are observed, some filled with glassy mucus, others empty. These are but bronchi passing through the collapsed tissue to functional lung-tissue beyond it. Under the microscope the tissue much resembles the fetal lung, is free from coal-dust, is highly vascular, contains here and there remnants of alveolar epithelium. In atelectatic lung-tissue the alveolar epithelium returns to its embryonal cylindric form.

Emphysema.—Emphysema is a chronic condition in which the pulmonary tissue is abnormally inflated with air. It may be a local affection of the air-cells in the distribution of a single bronchiole, or may be universal. By the majority of authors the term emphysema is restricted to the chronic process in which, together with inflation of the alveolar tissue, there are disappearance of the septa and loss of capillaries. Emphysema is also carelessly used to describe any inflation of the lung.

Local Emphysema.—Vesicular inflations are quite common in acute and chronic bronchial catarrh. The theory of their formation is that the swelling of the mucous membrane of the bronchus, or the secretion accumulated within it, while insufficient to check the forcible entrance of air into the vesicular tissue during inspiration, is sufficient to prevent the less forcible escape of air during the more passive expiration.

The gross morbid appearances are characteristic. The dilated lobules of the lung are pale, often without pigment, anemic, and form upon the pleura conspicuous rounded projections of bladder-like appearance if old, of spongy appearance if new.

In the acute inflation of the lung there are no permanent anatomic alterations, and when the bronchial obstruction is removed the air passes out and allows the lung-tissue to return to the normal condition.

A similar condition—acute vesicular emphysema—of greater extent, and quite as apt to be lobar as lobular, sometimes has a very different origin. When from any cause, as tuberculosis, the passage of air into considerable areas of lung-tissue is prevented, the inspiratory movements draw an excess of air into the pervious portions, which in consequence suffer distention and inflation.

The morbid appearances are like those of the preceding form. This *compensatory* or *vicarious* emphysema is liable to become chronic, because the conditions bringing it about are permanent.

The *chronic local emphysema*, called by Ziegler and others the *chronic substantial emphysema*, follows persistent or repeated attacks of the acute forms. It may also occur as a primary affection in those whose pulmonary tissue has an abnormally feeble resisting power, and is sometimes met with in nutritive disturbances, marasmus, and senility, without the preceding

changes. The chronic form of the disease is characterized by changes in the interalveolar, interinfundibular, and interlobular septa. The air-cells being so abnormally stretched not infrequently rupture and atrophy, or atrophy and rupture, it still being a matter of some doubt just which is the primary change, and thus cause the formation of single large air-spaces out of numerous small ones. This union of air-cells and loss of septa may go on to such an extent as to produce upon the surfaces of the lung, in the auricular appendix of the left lung, along the inferior borders of the lower lobes and sometimes upon the upper lobes, rounded bladder-like dilatations as large as a pigeon's egg. These air-bladders are almost entirely without septa, are conspicuous from their perfectly white color, and seem to have lost all the pigment that must at one time have been deposited in the tissue, and to be without capillary blood-vessels.

The destruction of the interalveolar septa is a matter which, as has been suggested above, is still rather uncertain in its exact stages.

Ziegler says the atrophy of the alveolar walls begins at their thinnest part and is accompanied by separation and disappearance of the elastic fibers. Grawitz suggests that the first step in the process is a transformation of the fibers of the alveolar walls to cells, and consequent feeble resisting power.

Issaksohn thinks the change originates in vascular disturbances. From the information at present obtainable, it seems to be fairly well established that the increased air-pressure is the first cause, and that rupture of the septa destroys the capillaries secondarily.

The lack of pigmentation in the emphysematous areas is of some interest. It is too complete to allow the inference that in the stretching process the individual particles of coal-dust are so removed from one another as to give the tissue a paler hue. Many of the emphysematous patches are white. Virchow at first expressed the opinion that the emphysema had taken place before the lungs became pigmented at all. As, however, grayish-white, pigment-free emphysematous patches are exceedingly common in the lungs of old people and quite rare in those of the young, we must conclude that the emphysema occurs late in life, and certainly after the pulmonary tissue has been pigmented. Grawitz taught that the pigment-cells wander out of the emphysematous tissue and return to the lymphatic and blood-vessels. Birch-Hirschfeld is of the opinion that it is liberated and in large measure expectorated, the remainder being removed by the wandering cells.

The epithelial cells of the alveoli take no part in the processes described. There may, however, be a concomitant catarrh in which many are desquamated, and sometimes fatty changes occur. In the remaining septa there are also occasional inflammatory infiltrations, but they are simply accidental, and have nothing to do with the major process.

There must be a limit to the amount of inflation to which the pulmonary tissue, with all its elasticity, can be subjected. We find, in fact, that it not rarely happens that the distended air-cells rupture. When this is so, air sometimes escapes from the normal air-containing tissue into the interalveolar tissue of the lung and causes the so-called *intervesicular emphysema*. Accidents of this character are said to occur most frequently when violent cough is present. Fatal issue may follow.

The ruptured alveoli are usually situated in the anterior portion of the upper lobe. The escaping air enters the interstitial tissue of the lung in globules varying in size from a pin-head to a bean. They gradually work

their way through the tissues to the hilus of the lung, and finally get into the fatty tissues of the mediastinum, where they are absorbed.

Senile emphysema is generally of the marasmatic form, though the chronic bronchitis from which old people often suffer may have much to do with it.

In chronic bronchial catarrh the local emphysematous patches that occur are not necessarily all of the same kind, especially if the catarrh depend upon some cause, as tuberculosis, associated with consolidation of the pulmonary tissue. In such cases the obstructed bronchi prevent the entrance of air into certain areas, and the consolidated lung-tissue predisposes to compensatory emphysema from overdistention of the remaining lung-tissue. Part of the vicariously inflated tissue may become further inflated by bronchial secretions, preventing the exit of the readily entering air.

Diffuse or General Emphysema.—The chronic diffuse emphysema is a process generally common to both lungs. It is more common in men than in women, and is usually found in adults about thirty to forty years of age. The most common cause seems to be chronic bronchial catarrh, but among the many causes to which it has been attributed we may enumerate hereditary tendency, congenital conditions and malformations, bronchial catarrh, diminution of the caliber of the bronchial tubes, chronic cough, diaphragmatic pressure from constipation, etc., excessive mountain climbing, continual singing or crying, stenosis of the nasal passages, and the playing of wind-instruments. Doubtless each has its weight of influence upon the individual case.

Osler is of the opinion that the mechanic theories are insufficient to explain the development of this disease without a preceding weakness or malnutrition of the pulmonary tissue.

As has been remarked, the common cause of emphysema seems to be chronic bronchial catarrh of the finer tubes associated with violent cough. In such a condition, the glottis being closed and the chest-walls contracted, the intrapulmonary tension is greatly increased, and finds its only relief by the dilatation of the air-cells.

When the disease is of long duration it is accompanied by a characteristic deformity of the thorax, which becomes remarkably rounded—barrel-shaped. The costal cartilages are lengthened and often calcified, and they and the sternum are pushed forward.

When the thorax is opened the lungs fail to collapse, but are conspicuous by their large size and projecting borders, which nearly or quite conceal the heart. The lungs are not only large, but are inelastic and do not collapse. Crepitation is diminished and the organs are soft and flaccid. The pale color and loss of pigment mentioned under Local Emphysemas are observable. Upon close inspection one can observe beneath the pleura a large number of air-vesicles greatly enlarged, forming bladders from the size of a pin-head to that of a pea, and projecting from the free borders of the lung, which are irregularly rounded air-bladders as large as a pigeon's egg. The walls of these air-bladders are thin, sometimes semitransparent, without pigment, and anemic. In some of the air-bladders remnants of the interalveolar septa may be found.

Some of the largest air-bladders sometimes occur at the root of the lung, on the inner surface of the lobe. Generally the conspicuous bladders are at the anterior inferior margins of the lobes.

Microscopically the lungs present the enlargement of the air-cells, loss of septa, and disappearance of capillary blood-vessels already described in speaking of the local emphysemas.

Secondary changes of importance are also observed. The bronchial tubes are dilated, sometimes ectatic, and show the lesions of chronic bronchitis. The heart is also affected, its right auricle and ventricles being both dilated and hypertrophied, the tricuspid opening enlarged, and the valves rather sclerotic.

Circulatory Disturbances.—**Acute congestion** of the lung may occur from the inhalation of certain irritating gases, hot or cold air, and from toxic substances circulating in the blood, extensive burns, etc. It is also the first manifestation of the acute inflammatory diseases of the lung itself. Sometimes, when the circulation is obstructed, as by an embolus, a *collateral hyperemia* of the rest of the organ follows. The condition usually is general; sometimes it apparently causes death.

In cases dying with acute congestion of the lungs, the organs are found

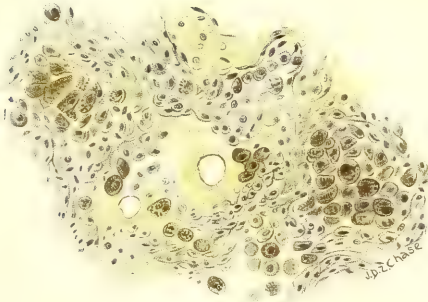


FIG. 271.—Brown induration of the lung, from a case of obstructive heart disease, showing the air-cells occupied by desquamated epithelial cells pigmented with pigment (hemosiderin) from the destroyed red blood-corpuscles. $\times 240$.

to be swollen, more firm than normal, uniformly dark red in color upon the cut surface, and relatively poor in contained air. The capillaries are dilated. A serosanguinolent exudate occupies the air-cells, the numerous red corpuscles probably escaping from the vessels by diapedesis. When the organs are incised large quantities of bloody fluid, which becomes frothy when the lung is pressed, escape.

Chronic congestion of the lung is much more common than acute congestion. It occurs whenever there is a mechanic obstruction to the return of the blood from the lungs to the heart. A variety of it called *hypostatic* congestion is due less to mechanic obstruction than to circulatory weakness, and is seen in slow fevers and in adynamic states generally.

Hypostatic congestion is one of the most frequent postmortem conditions. The lungs are larger than usual, dark brown in color, and unusually firm. The ordinary forms are chronic, and are associated with such permanent changes as fibroid induration and pigmentation. It is the presence of connective tissue that makes the tissue so resistant. Pearce has recently shown

that the elastic tissue of the lung is also increased in passive congestion. The chronic congestion associated with induration and pigmentation is called *brown induration*. It is characterized histologically by the congestion with distention of the capillaries, thickening of the interalveolar septa, in which embryonal connective tissue as well as additional fully formed fibers can be made out, by the pigmentation of the interalveolar tissue, and by a catarrhal condition of the alveoli, in which the epithelial cells are desquamated and accumulate in the air-spaces. The desquamated epithelial cells are nearly always pigmented. The pigmentation depends upon the liberation of blood-pigment from the corpuscles, which, having escaped from the capillaries, disintegrate in the air-cells. The pigment thus set free is taken up in part by the alveolar epithelium, in part by leukocytes, in part by the returning currents of lymph, and thus finds its way into the interstitial tissue of the lung. A certain amount of the pigment is expectorated, as can be determined by a microscopic examination of the sputum, in which alveolar epithelial cells and leukocytes loaded with the granules are abundant.

In hypostatic congestion, which is a more acute process, no connective tissue forms. The congested tissue is always the dependent part of the lung. It is boggy to the touch, dark blue-red in color, and heavy. This condition is found microscopically to be accompanied by a sanguinolent accumulation in the air-cells, the erythrocytes disintegrating and liberating pigment. The condition is described also as *splenization* of the lung.

Anemia of the lung is usually local, and depends upon obstruction of the vessels. It may form a part of general anemia.

Edema of the lung, characterized by the presence in the air-cells, bronchioles, and bronchi of a serous blood-stained fluid, is an exceedingly common condition. It may affect a part of a lung, a whole lung, or both lungs. The tissue affected is increased in size, boggy to the touch, heavy in specific gravity, pale or dark in color, more or less hyperemic, and when incised allows the escape of a clear blood-stained, air-mixed fluid in considerable amount. When localized the condition is most common in the lower lobes. Examined microscopically the fluid contains erythrocytes, some leukocytes, a good many desquamated alveolar epithelial cells, and pigment-granules.

The condition is most common as congestive edema resulting from passive congestion and occurring in the dependent parts of the lung in conditions of cardiac weakness and failure.

It may be due to septic or toxic conditions, and may arise from the inhalation of irritating substances, from inhalation of hot or cold air, from nephritis, from exposure, and a great variety of causes.

An edema with marked hyperemia also sometimes occurs in the early stages of some of the inflammations of the lung, and is characterized by marked catarrhal desquamation of alveolar epithelium and the presence of albumin in considerable quantities. The precipitation of the albumins of this exudate, when the lung-tissue is placed in hardening reagents or boiled, gives a granular appearance to the alveolar contents.

Hemorrhage of the lung is of frequent occurrence. The hemorrhages may be divided into those occurring by rhaxis and those occurring by diapedesis, although it is quite impossible to make a sharp distinction between the two.

Punctiform hemorrhages frequently form part of pulmonary inflammations and infections, disturbances of circulation, and the hemorrhagic

diathesis. Small septic infarcts and areas of violent bronchopneumonia may be characterized by hemorrhages of small size.

Larger hemorrhages occur from traumatism, tuberculous and cancerous erosions of blood-vessels, and the bursting of small aneurysms in tuberculous cavities.

The escaping blood may occupy the interstitial tissue or may be found in the air-cells and tubes.

When the escaped blood is in considerable amount the tissue becomes saturated with it, and the replacement of the air by the bloody serous accumulation transforms the lung-tissue into a pulpy, blackish-red, soft, lacerable tissue, which from its resemblance to the tissue of the spleen is described as *splenization*.

Hemorrhages by diapedesis—so called—occur in consequence of hyperemias, from the abnormal circulatory conditions, of cardiac weakness, from obstructive heart affections, hemophilia, scurvy, and certain infectious diseases, such as scarlatina, typhoid fever, variola. It may also occur in cerebral diseases associated with respiratory disturbances.

Instead of causing circumscribed infiltrations of the pulmonary tissue, the effect of the hemorrhages by diapedesis is more to fill up the air-cells with a serosanguinolent fluid, and thus produce a *bloody edema* or *hypostatic congestive edema*, such as is common in the obstructive heart diseases and in cardiac failure. When inflammations occur in cases of hypostatic congestive edema, as sometimes happens, the condition is described as *hypostatic pneumonia*.

Hemorrhage from the lungs is known clinically as hemoptysis, and may vary from a slight discoloration of the sputum to the rapid expectoration of quantities large enough to cause the death of the patient. The blood is generally bright red and mixed with air.

The blood ordinarily escapes from the lungs through the bronchial tubes, but is subject to distribution by the movements of the air, and if not at once removed by cough and expectoration is likely to be aspirated into deeper parts of the lung, where it may fill up parts of tissue and cause the appearance under the pleura of dark-colored solid masses, which at first glance are easily mistaken for primary hemorrhages.

The recovery of hemorrhage occurs by the expectoration of part of the extravasated blood and the absorption of the remainder. In the absorption process the red corpuscles are destroyed, and their pigment, being liberated, follows the same course as that described in brown induration, being broken up in part by the alveolar epithelium, in part by leukocytes, in part by currents of lymph. The granules are finally expectorated or returned to the circulation through the lymphatics. As their final removal is slow, the tissue often remains pigmented for a long time.

Hemorrhagic Infarcts of the Lung.—The pulmonary infarctions generally result from embolism of the branches of the pulmonary artery. The emboli may come from thrombi in the right heart or in the systemic veins. The emboli lodge at the smaller bifurcations. The subsequent changes are those usual in hemorrhagic infarctions, and only occur where there is no collateral circulation.

The infarctions appear in the lung as rounded, often conical, dark, blackish-red consolidations, seen most distinctly on the pleural surface toward which the bases are directed, and rather distinctly circumscribed from the

surrounding hyperemic pulmonary tissue. In size they vary from a pea to a hen's egg. Upon the pleura there is often a fresh local inflammation, shown by a fibrinous deposit. Such fibrinous deposits are most frequent in infarcts that have been formed for some time. The consolidation of the tissue is due to the entrance of the blood into its interstices and into the air-cells.

The termination of the process of infarction is important. When the hemorrhagic infarction is small and the tissue able to retain its vitality, the softening and absorption of the coagula may progress to a final restitution of the tissue. Possibly the exact normal condition is not attained, as a pigmentation and slight induration may remain.

When larger the infarctions are likely to be followed by necrosis of the tissue from malnutrition depending upon cessation of the circulation, the tissue being occupied by the extravasated blood. The further course of the process will then depend upon accident. If bacteria enter the necrotic tissue, gangrene or suppuration may follow, and produce marked destruction of tissue. If, however, the tissue remains uninfected, reactive inflammation accompanied by connective-tissue formation takes place, and the destroyed tissue is replaced by a cicatrix appearing later in the life of the individual as a pucker upon the pleural surface of the lung. When incised, a band of fibrous tissue is found to descend a short distance into the lung-tissue.

The process of organization does not mean the transformation of the necrotic infarction into connective tissue, but its gradual replacement by connective tissue forming at the periphery, pressing upon it, and taking its place as it is absorbed. In some hemorrhagic infarctions it is quite possible to see the necrotic tissue surrounded by its newly formed connective-tissue capsule.

When the embolus is infectious, suppuration modifies the sequence of events.

In rare cases hemorrhage occurs into the lungs as well as other thoracic and abdominal organs in consequence of diseases of the brain. This was first observed by Brown-Séquard, and afterward confirmed by Nothnagel. In cerebral apoplexy and brain-tumor congestion and hemorrhages into organs occur on the hemiplegic side. Brown-Séquard attributed the condition to the sudden contraction of the smaller arteries and veins of the affected part, by which the blood-pressure in the capillaries would suddenly rise to so high a degree that rupture of their coats must result. Nothnagel observed that such hemorrhagic conditions could be so exaggerated that the hemorrhage would embrace nearly the whole lung.

Gangrene of the lung, while almost never a primary affection, is so well characterized that it must be described independently of the conditions to which it is secondary.

The causes of the affection are numerous, and include such destructive lesions as favor the entrance of bacteria into tissue of diminished vitality. Rare cases, occurring in individuals addicted to the abuse of alcohol, are without any obvious cause, and are said to be *idiopathic*. Their exact nature is not thoroughly understood. Other important causes are as follows:

Pneumonia, tuberculosis, and carcinoma, with widespread inflammations and interstitial and alveolar hemorrhages, are frequent causes.

Embolism, especially when the emboli are infectious or when extensive hemorrhagic infarctions with subsequent infection follow it.

Inspiration of fetid substances from higher portions of the air-passages, as in gangrenous and phlegmonous inflammations in the larynx.

Perforation of ulcers of the esophagus and other organs into the lungs and the entrance of foreign matter into the pulmonary tissue.

Traumatism from the entrance of irritating "foreign bodies" into the lung.

Ever since the days of Laennec it has been customary to recognize two forms of the disease:

Circumscribed gangrene, which occurs in the form of larger or smaller rounded masses, not rarely multiple, and upon section appearing as dark-brownish, greenish, or blackish dry tissue-remnants surrounded by an area of hyperemia. When older there may be a distinct reactive inflammation. When the gangrene spreads the surrounding tissue may be edematous or infiltrated with blood. When the gangrenous area touches the pleura, it produces localized pleuritis with a fibrinous deposit upon the diseased surface.

The gangrenous tissue gradually liquefies, beginning at the periphery, and is eventually transformed into a dissolved, bad-smelling, semifluid material with a few suspended tissue-remnants. Bronchi may pass through the gangrenous area, or may open into it and make a way for the escape of the contents by expectoration. Arteries that pass into a gangrenous area suffer thrombosis and obliteration; occasionally one is eroded and hemorrhage occurs.

The gangrenous area may spread by producing reactive inflammatory changes, the granulation-tissue becoming infected and causing extension of the gangrene. More frequently the gangrenous area becomes encapsulated and proceeds to heal, recovery being greatly facilitated by the escape and expectoration of the decomposed matter through a bronchial tube. In the process of expectoration, however, putrid bronchitis and other secondary changes are likely to occur.

Rupture of a gangrenous focus into the pleural cavities may lead to pleuritis, to pneumothorax, etc.

Diffuse gangrene may result from extension of the circumscribed form by the inspiration of the putrid material into new areas of lung-tissue, or may follow certain diseased conditions, as pneumonia, as a secondary process.

The diseased tissue is greenish black, soft or dry, or mushy. There may be various communicating cavities.

Death may occur from septicemia, or from septic thrombosis and embolism.

Pneumokoniosis.—The lungs of the adult differ from those of the infant in containing larger or smaller, blue-black, subpleural pigmentations irregularly distributed upon the lung, giving it a mottled appearance. The discolorations consist of deposits of fine particles of inhaled soot, dust, and other pulverized materials with which the individual has come in contact, often in pursuit of his occupation. The color of the pigmented areas is generally black or blue black, but may vary with the chemistry of the substance causing them. The amount of pigmentation will vary according to the conditions producing it; thus, coal-miners and workmen employed in lampblack manufactories, because of the constant exposure to dust-polluted atmospheres, are more likely to have greatly discolored lungs than men whose

pursuits are more cleanly. Infants not exposed to the causes of the pigmentations are without them.

Inasmuch as the majority of mankind from infancy to adult life are obliged to inhale atmospheres containing some dust, it has become the custom to regard the presence of a certain amount of it as normal. The amount of soot in the human lung is always more than in the lung of the lower animals, probably because few of the lower animals live in atmospheres made impure by fires, and often loaded with tobacco-smoke, or habituate factories in which iron-filings, glass-grindings, fullers' earth, and the like, are suspended.

When the amount of discoloration becomes excessive, there is not only pigmentation, but also induration of the pulmonary tissue, and its integrity is lowered.

Pneumokoniosis is a diseased condition of the lung resulting from the inhalation of dusts. It is an affection chiefly met among those whose occu-

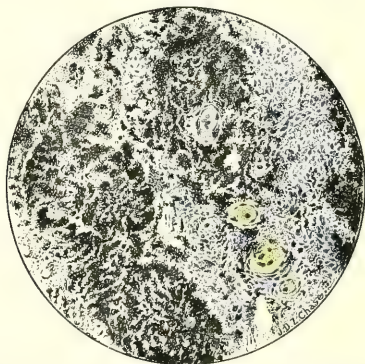


FIG. 272.—Anthracotic lung. The black areas consist of coal-dust deposited in the connective tissue of the lung, which is partly newly-formed, partly pre-existent. $\times 100$.

pations as coal-heavers, masons, plasterers, file-grinders, glass-cutters, potters, carpenters, cigaret-makers, jute-spinners, turners, scroll-sawyers, brush-makers, hair-dressers, and hat-makers, whose occupations confine them to atmospheres in which mineral, vegetable, and animal dusts are ever present. The effects of the dust are exerted upon both the bronchi and the walls of the air-cells.

Unless, as happens in hat-factories, where mercury is much used, wall-paper establishments, where arsenic is said to be common, and paint-factories, where the air is full of lead, the dust has pronounced chemicophysiological actions upon the organism, the effect of its presence is a local irritation caused by the contact of the foreign particles with the cells. Such irritative effect is seen in mild type all along the respiratory tract, upon whose mucous membrane the dust is deposited. A moment's thought will suggest that the cilia of the anterior nares act as a sieve for the exclusion of coarse particles, and will recall to mind the moist Schneiderian membrane, the laryngeal, pharyngeal, and tracheal mucous membranes with their mucous secretions, as

excellent surfaces for the collection and retention of dust-particles. Such, indeed, they are, and upon them, no doubt, large quantities of dust are deposited mixed with the secretions and ultimately expectorated. The sputum of pneumokoniotic patients always contains dust-particles, and continues to do so long after they are removed from the sources of contamination.

In spite of these protective arrangements, however, considerable quantities of the finer dust-particles enter the air-cells and are retained in the lung.

The further changes depend upon the nature and disposition of the dust-particles. If they are soluble, they are absorbed; if insoluble and not removed by expectoration, the leukocytes load themselves with the particles and proceed to convey them out of the pulmonary tissue into the lymphatics. The leukocytes reach the interstices of the interalveolar tissue and deposit the particles there, or they reach the lymph-nodes of the lung and the bronchial lymph-glands. The result is that dust is deposited in the lymph-vessels, in the interlobular, interalveolar, subpleural, pleural, perivascular, peribronchial, and bronchial connective tissues. The dust-particles may be free or enclosed in cells. The bronchial lymphatic glands may be much enlarged and entirely black from the amount of dust they contain. Ultimately, as Arnold, whose researches upon this subject are well known, has shown, the glands may soften, and by ulceration discharge their contents into the venous system, with the production of dust-emboli in the organs of the body.

As the condition varies somewhat according to the nature of the dust, it is customary to make subdivisions as follows:

Anthraxis—soot or coal-dust. The most common and least important form. Almost everyone has it more or less markedly. The pigment is most widespread toward the apices of the lungs and almost absent at the edges.

Siderosis—metal-dusts—oxids of iron especially. These dusts generally produce a brick-red color, though sometimes the color is black.

Chalcosis—stone-dusts—quartz and glass.

Kaolinosis—fullers' earth.

Alummosis—met with in workers in ultramarine and porcelain.

The stone- and metal-dusts are most injurious, and in addition to the catarrh produce a marked hyperplasia of the connective tissue, so that the lung-tissue may contain numerous fibrous, generally dark-colored nodules varying in size from a millet seed to a pea or even a cherry, and made up of concentrically arranged connective tissue surrounding what were probably originally lymph-nodes full of the inhaled dust. In the small nodules the connective tissue is arranged about a single center; in the larger nodes, about several separate centers. The lesion is thus found to be a true interstitial inflammation with resulting fibrosis.

In cases in which the nodules are few and scattered, the intermediate pulmonary tissue is normal except for its pigmentation. If, however, the nodules are numerous, the lung is indurated and fibrous, and considerable-sized areas are solid and empty of air (nodular pulmonary cirrhosis).

The nodes have two different starting points. They may represent destroyed and indurated alveolar systems, or they may form about the lymphatic vessels, and lie partly in the lung-tissue, partly in the peritracheal and perivascular tissues.

For an unknown reason, the most marked lesions seem to occur in the apical portions of the lung.

When there is much consolidation of the pulmonary tissue, vicarious emphysema may be present.

The pleura over the diseased areas is usually thickened.

The inhalation of some kinds of dust, especially metal-dust, seems to favor the development of pulmonary tuberculosis.

Inflammations.—Bronchopneumonia or Peribronchial Pneumonia.

—When in suppurative and gangrenous affections of the respiratory passages infectious or irritating material enters the smaller bronchial tubes, catarrhal capillary bronchitis generally results. The thin walls of the bronchioles permit only a mild degree of inflammation without transmitting it to the contiguous tissues of the lung and establishing a consecutive peribronchial inflammation in the tissues immediately surrounding the bronchiole, with possible further subsequent extension to the adjacent pulmonary tissue.

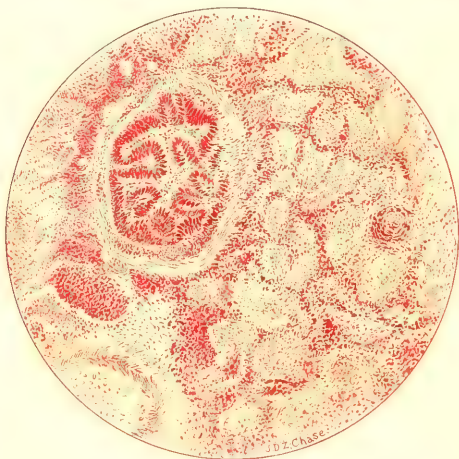


FIG. 273.—Pneumonia and suppurative lymphangitis. $\times 150$.

This causes a localized pneumonia, which conforms more or less to the area of distribution of the bronchiole, and suggests the name *lobular pneumonia*. The irritating material may also be inspired directly into the infundibulum and air-cells, and thus cause the lobular pneumonia. The fusion of a number of areas of the kind described occasionally leads to the inflammatory involvement of an entire lobe.

The extent and severity of the affection vary greatly with the character of the inspired materials. Sometimes the disease runs a slow, mild course; sometimes it is suppurative or even gangrenous, and produces extensive destruction of the peribronchial and infundibular tissues.

When a lung the seat of bronchopneumonia is examined with the naked eye, its appearance is found to vary considerably. In the early stages and in the simple cases the lungs are somewhat hyperemic, and show at numerous points small yellowish-gray areas encircling the bronchioles, whose lumen,

diminished by the inflammatory swelling, appears as a dark point or minute opening in the center. Here and there, where actual invasion of the alveolar tissue has occurred, there may be consolidated areas of larger size, corresponding to the groups of infundibular tissue forming a lobule. These pneumonic areas are hyperemic, and are at once detected by their solid nature.

If the disease is advanced and widespread, the lung presents a rather interesting appearance from the variety of involved processes going on in different portions. The organ has a rather marbled appearance from alternating areas of air-containing, hyperemic lung-tissue, red consolidated bronchopneumonic patches, and purple atelectatic areas from which the entrance of air has been prevented by inflammatory processes. There may also be numerous pale areas of compensatory emphysema.

The bronchopneumonic patches, when incised, are consolidated and the



FIG. 274.—Section through a bronchiole, showing acute peribronchitis with leukocytic infiltration of the surrounding tissues. $\times 125$.

air-cells filled with a reddish exudate. Around the borders of the patch a zone of hyperemia may be observed.

Microscopically the submucous tissues, and indeed all the subjacent tissues, may show a round-cell infiltration. In the bronchopneumonia, a catarrhal inflammation of the surrounding air-cells and an accumulated exudate, made up in part of outwandered leukocytes and in part of desquamated epithelium, are present. Among the cells there are sometimes threads and reticula of fibrin, but the presence of much fibrin is the exception, not the rule, in the bronchocatarrrhal pneumonias. The catarrhal character of the exudate led to the old name *catarrhal pneumonia*.

The disease may be fatal or it may end in recovery. In mild cases recovery is simply a matter of absorption and expectoration. In more serious cases there may be lost tissue to replace, or the duration of the disease, if continued, may produce organization and fibroid indurations in some of the patches.

The disease is quite common in the posterior or dependent portions of the lungs of persons of enfeebled vitality suffering from chronic diseases, and is probably due to lack of normal resisting power of the lung to what would be under normal conditions very mild irritations. Because of its position, this form of the pneumonia of the dependent parts of the lung is spoken of as hypostatic pneumonia.

The causes of bronchopneumonia are varied. Roughly stated, they are due to the inspiration of any irritating substance. They are due sometimes to dusts, as in pneumokoniosis, sometimes to the action of bacteria. From the inspiration of the specific bacteria or of other bacteria accidentally present, they also frequently occur in infectious diseases, as diphtheria, measles, pertussis, influenza, etc. The pneumonia bacillus is probably the most common cause, and Smith has reported several cases in which Friedländer's bacillus has produced pneumonic conditions, in which the bacilli formed a very conspicuous part of the accumulated products in the air-cells.

Acute Fibrinous Pneumonia (*Lobar or Croupous Pneumonia*).—Acute fibrinous pneumonia is an acute infectious disease, usually characterized by a local inflammation in the lung and grave constitutional symptoms.

The disease is caused in nearly all cases by the *Micrococcus lanceolatus* (*Diplococcus pneumoniae* or *pneumococcus* of Fränkel and Weichselbaum), which, when favorable conditions arise, grows luxuriantly in the inflamed portions of the lungs, and distributes its toxin through the circulation.¹ A certain parallelism exists between pneumonia and diphtheria, both diseases being characterized by infection, local areas of inflammation with fibrinous exudation, and constitutional symptoms resulting from a toxin; the *Micrococcus lanceolatus* gains entrance into the circulating blood more commonly than the diphtheria bacillus.

The exciting cause of pneumonia is without doubt the pneumococcus, yet the specificity of the micro-organism is difficult to prove, because of its common occurrence in the respiratory passages of healthy individuals. Indeed, the pneumococcus was first observed in the saliva of healthy men, and its subsequent recognition as an important factor in the disease was rather a surprise.

What causes determine that the pneumococcus, so common in the mouth, shall descend to the alveolar tissue of the lung and set up so violent an inflammation as that of pneumonia, have not yet been determined. As usual, "cold" is supposed to be one of the most common causes. Diminished vital resistance, such as results from Bright's disease, alcoholism, etc., is also a marked predisposing factor. The frequency of pneumonia in alcoholism and its fatality under these circumstances are known to every clinician.

The disease has a sudden onset, with chill and fever, followed almost immediately by a series of well-marked anatomic changes.

In 100 autopsies upon cases of pneumonia, Osler found the entire lung affected 27 times, the lower lobe affected in 34 cases, the upper lobe in 13 cases. The right lung was diseased in 51 cases, the left in 32 cases, both lungs in 17 cases. According to statistics of the "Rudolphstiftung" in Vienna, in 7747 cases, 52.78 per cent. were of the right side, 37.46

¹ For a discussion of the bacteriology of acute fibrinous pneumonia, see Curry, *Jour. of Exp. Med.*, iv., 169, 1899.

per cent. of the left side. Usually it is the lower lobe of the lung that becomes diseased.

The first changes consist of a marked turgescence of the interalveolar capillaries of the lung, followed by the escape from them of a viscid, reddish serum that occupies considerable of the breathing-space. This period is usually described as the stage of "congestion."

The lung in this stage of the disease appears distinctly enlarged; is dark red in color and firm to the touch. It crepitates less than normal. Upon section, frothy red liquid can be squeezed from the alveolar structure, the tissue seems decidedly less spongy than normal, and is heavy. It will not sink in water until the disease has progressed beyond the stage of congestion to that of consolidation.

Exactly in what order the changes of pneumonia take place is a question. For many years it has been the custom to describe a regular course with stages of congestion, red hepatization, gray hepatization, and, later,

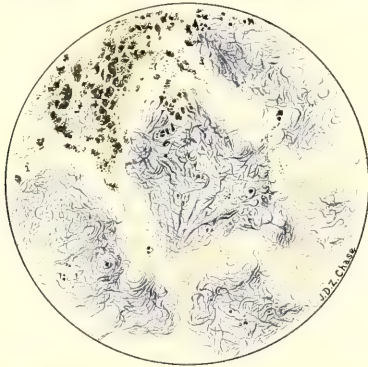


FIG. 275.—Croupous or fibrinous pneumonia, stage of red hepatization: stained by Weigert's method to show the fibrin only. The blue threads filling the air-cells consist of fibrin-filaments. $\times 180$.

resolution. Baumgarten seems to have first shown this to be erroneous, and Eichhorst reported a case of an old woman dying in the Zurich clinic, in whose lung gray hepatization was encountered when red hepatization was expected.

In reality the course of events is not only somewhat variable, but the successive invasion of different contiguous portions of the lung makes it common for the same lung to exhibit numerous instead of single stages of the disease.

There can be no doubt that the disease begins as described, with congestion, followed by consolidation. From the resemblance which the consolidated lung bears to liver-tissue, this process is called *hepatization*. In this stage, when typical, the air-cells, which heretofore admitted some air in spite of the transuded serum, are completely filled with the products of inflammation, in which a characteristic coagulation or fibrin formation takes place. When the exudate is rich in erythrocytes, as is nearly always the case, and in consequence red in color, the hepatization is spoken of as *red*

hepatization. The lung in this stage is large, heavy, solid, dark red, and friable. The cut surface has a granular appearance, and when pressed allows the escape of some bloody serum, but no air. Frothy, viscid mucus may occupy the bronchial tubes. When scraped with a knife, the contents of the air-cells appear upon the blade as minute free fibrinous plugs. Cut fragments of the tissue sink readily in water.

Microscopically the air-cells are found to be entirely full of a coagulated inflammatory exudate. The conspicuous components of the coagulum are

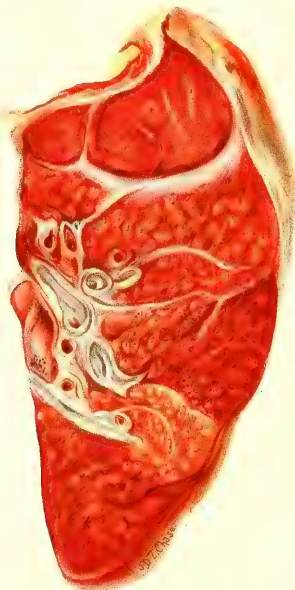


FIG. 276.—Lung of a child, showing the appearance of the organ in the stage of red hepatization of croupous pneumonia. The pneumonia has been preceded by chronic pleuritis, which accounts for the thickened fibrous trabeculae extending into the tissue, and which may have had something to do with the peculiarly prominent appearance of the bronchioles throughout the lung (from a specimen loaned the writer by Dr. Joseph Sailer).

its many erythrocytes and the fibrin, whose fibrils form a reticulum extending among the cells. There may be so much fibrin in the early stages that the air-cells look as if occupied by tufts of cotton-wool in whose meshes the cells have been caught.

In addition to the fibrin, which can be beautifully demonstrated by Weigert's stain, there are large numbers of red and white blood-corpuscles and desquamated alveolar epithelium. The pneumococci are also present in large numbers, many of them in the protoplasm of the leukocytes.¹

Ordinarily, red hepatization terminates by the gradual subsidence of the

¹ The histology of acute fibrinous pneumonia is described by Pratt, *Jour. Boston Society of Med. Sciences*, iv., 183, 1900.

hyperemia, and the liquefaction of the fibrin and such red corpuscles as have been caught in its meshes. The period of softening is one in which the leukocytes crowd into the air-cells, and can be found incorporating the bacteria and odds and ends of cells and fibrin. The loss of red cells, the cessation of the hyperemia, and the advent of leukocytes bring about a change in the color of the affected part, its redness passes away and it becomes grayish in color—*gray hepatization*.

Both forms of hepatization may exist at the same time in contiguous parts of the lung. In microscopic sections it may be impossible to tell from the appearances presented whether the tissue was taken from a gray or a red hepatization.

The gray hepatization begins the process of recovery, and with its development the lung-tissue becomes softer. Shrinking and softening of the exudate soon allow some air to enter. Frequently fibrinous plugs are formed in the bronchial tubes and block them up, keeping the air out of the air-cells otherwise ready to receive it. Shrinking and softening must detach these and permit them to be expectorated before air can reach the alveolar structure.

The ultimate restitution of the lung takes place partly by expectoration and partly by absorption. Portions of the softened exudate are taken up by the lymphatics, others carried away by the activity of the leukocytes. The separation of the fibrinous plugs from the walls of the air-cells takes place in fatal cases in from seven to ten days. Recovery takes from two to four weeks, sometimes longer.

The inflammatory process of the air-cells does not occur independently of the pulmonary tissue, and in all cases the interalveolar septa are edematous and infiltrated with round cells.

The cells infiltrating the lung-structure disappear at the end of the inflammatory process by absorption through the lymphatics.

The portions of the lung contiguous to pneumonic areas are nearly always hyperemic; they may, however, be pale or edematous. The bronchial lymphatic glands are swollen, moist, red or gray. The bronchi are nearly always inflamed and contain a red or reddish-brown mucous or sero-mucous secretion.

The pleura is always affected, and appears thickened and opaque, and has a fibrinous exudate upon its surface. There is nearly always a pleuritic effusion, the fluid containing pneumococci. The effusion is absorbed about the same time as the alveolar contents, and as respiration is again established and the fluid leaves the chest the pulmonary and parietal pleuræ not infrequently come in contact and unite by adhesions.

In fatal cases the cavities of the heart may be occupied by most tenacious clots, which, with their branched extensions into the vessels, can be drawn out to considerable length.

Pneumonia is frequently secondary to typhoid fever, measles, influenza, and other infectious diseases, and in its turn is the starting point for numerous secondary infections, sometimes of great importance. For example, pericarditis, endocarditis, meningitis, and inflammations of the soft parts of the pharynx, soft palate, and nose occur, and may lead to most serious consequences. Croupous colitis has been seen as a complication by Bristowe.

It has been stated that pneumonia may be secondary to other infectious diseases. When this is the case the pneumonia may be caused by the

pneumococcus or by streptococci, influenza bacilli, or other bacteria. The spontaneous cases, however, seem always to be due to the pneumococcus.

The recovery from pneumonia may be delayed to the tenth week in certain atypical cases.

The most unfavorable outcome of the disease is probably gangrene of the lung. It occurs particularly when there have been interstitial hemorrhages, when the pneumonia is particularly malignant, or when secondary to some violent suppurative or putrid lesion.

Abscess of the lung may also succeed pneumonia. Certain rare cases of pneumonia do not progress to a recovery by resolution, but become chronic, and are followed by induration of the lung. Osler met this condition only once in 100 autopsies. The appearance of the lung after four to ten weeks is flesh-like, red, and tough (carnified), the cut surface smooth.

When examined microscopically it is found that active cell proliferation and tissue organization are in progress everywhere. The condition is a chronic productive inflammation of the lung, with marked production of connective tissue, partly by new formation of vascularized granulations in the interior of the alveoli, partly by hyperplasia in the interalveolar walls. Here and there fibrinous plugs will be seen partly replaced by connective tissue; other alveoli are found filled by newly formed connective tissue.

There is a simultaneous hyperplasia of the connective tissue of the bronchial, peribronchial, perivascular, interlobular, and pleural connective tissue, leading in the course of time to pulmonary thickening and induration as well as to pleuritic adhesions (Ziegler). When the alveolar epithelium is lost there is nothing to prevent the new tissue within the alveolus from uniting with the alveolar walls, and in this way solid connective-tissue masses form in the lung. In other places a glandular appearance occurs from the simultaneous growth of both connective tissue and epithelium, resulting in small circumscribed spaces containing cuboid epithelium.

The distribution of the induration is rather variable. It may be general throughout the pneumonic area, may occur in solid patches or in the form of trabeculae traversing the lung. The tissue is not circumscribed, but blends gradually with the normal lung-tissue.

Over the indurated area the pleura is thickened. If the patient live, contractions with resulting deformities, bronchiectasis, and emphysema occur.

Pleurogenic Pneumonia.—Pleurogenic pneumonia is inflammation of the lung secondary to inflammation of the pleura. In all cases of pleurisy the lung is more or less severely affected by continuity of tissue and lymphatic invasion along the septa or bronchial vessels.

The pleurogenic pulmonary inflammations are therefore interlobular, perivascular, and peribronchial, and are for the most part due to bacterial invasion from the pleural lesions.

The lesions may be acute and characterized by purulent infiltration of the connective tissue, so that on section the lung is seen to contain yellowish or grayish-yellow bands irregularly distributed here and there, most marked where the separation of lobes and lobules is imperfect, and noticeable about the veins. When the disease affects the bronchioles, they are seen to be surrounded by circumscribed purulent collections. There may also be bronchitis. The infiltrated tissue is in a thickened, somewhat softened, yellowish or whitish condition.

A variety of the process in which the suppuration progresses to the

extent of actually dissecting the lobules one from another is described by Ziegler as *dissecting pneumonia*.

The great mass of the lung-tissue is normal, or somewhat congested. Such parts as are pressed upon by the infiltrated tissue are empty of air, dark red, and carnified.

When recovery takes place the collected exudation may be absorbed, but the lung rarely, if ever, regains its normal appearance, a considerable thickening of the affected tissue generally remaining. If the pleuritis become chronic, the pleura not only thickens in consequence, but the pulmonary connective tissue—interlobular, peribronchial, and perivascular—undergoes marked hyperplasia, so that bands of connective tissue appear to extend through the lung in various directions.

In many forms of pleuritis the lung is compressed by the inflammatory effusion. The absorption or evacuation of the fluid may not then be followed by a return of the lung to its normal size, because of the unyielding connective tissue it contains in consequence of pleurogenic changes.

In such cases a more or less widespread atelectasis, local areas of emphysema, bronchial catarrh and bronchiectasis, fibroid thickening of the pleura and septa, and loss of breathing space result. Later, deformity of the chest and even curvature of the spine may develop.

Hematogenous Pneumonia.—This form of pulmonary inflammation is caused by microbial embolism of the pulmonary vessels. It is of regular occurrence in pyemia, and of greater or less severity in different cases. The infectious emboli may be small, or of sufficient size to plug the vessels and bring about hemorrhagic infarctions.

When hemorrhagic infarction takes place in consequence of the embolism, the suppuration is best seen about the infarction as a yellowish or grayish zone sharply circumscribed from the surrounding lung-tissue.

As the infarct undergoes necrosis and softening it becomes infiltrated with pus and forms a pulmonary abscess. Gangrene may follow the entrance of putrefactive bacteria into the infarcted area, the appearances then being, in the main, like those of ordinary gangrene.

When too small to produce infarctions, the lodgement of cells containing pus organisms, or the collection of the pus bacteria in the capillaries of the lung itself, causes small areas of inflammatory infiltration that develop into small abscesses. The air-cells contiguous to the affected capillary are found on microscopic section to be filled with an exudate consisting of small round cells, fibrin, desquamated alveolar epithelium, and rich in pyogenic bacteria.

If the inflammation be subpleural the pleura becomes affected, and an

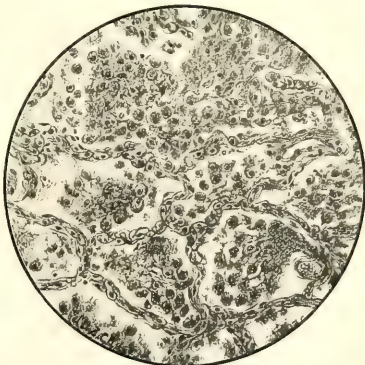


FIG. 277.—Acute septic pneumonia following a case of gunshot wound. $\times 140$.

empyema can result from rupture of the abscess and liberation of the pus organisms in the pleural cavity.

The involvement of the pleura is important, because when empyema, or any condition of the pleura in which many bacteria are present in the pleural cavity, develops, conditions are favorable to the further extension of the disease into the lung by absorption of bacteria through the bronchial, peribronchial, and interlobular lymphatics, the production of a suppurative lymphangitis, and, later, numerous destructive changes.

Abscesses in the lung may empty into the pleura or into a bronchial tube. When the rupture is into the pleura, empyema is almost certain to follow. If, on the other hand, the rupture is into a bronchial tube, it is scarcely more favorable, for in the majority of cases the aspiration of the infectious material into fresh areas of the lung brings about bronchopneumonia. The pus may be absorbed, or calcification may take place in the inspissated contents of the abscesses.

Tuberculosis.—Tuberculosis of the lungs is one of the most common and most fatal diseases. It affects all ages except early childhood, both sexes and all occupations, and occurs in all the walks of life. In many cases it is a progressive, destructive disease with a fatal termination. In not a few cases spontaneous recovery seems to occur.

The disease is caused by the tubercle bacillus, which finds its way into the lungs either by the circulation or by the inspired air.

Much discussion has been held upon the important question of relative frequency in these modes of infection. Some assert that beyond doubt the bacillus is originally ingested, finds its way through the lacteals to the thoracic duct, then to the venous circulation and the lungs; while others hold that the bacillus is inhaled directly into the lungs.

There seems to be little room to doubt that the inspiration theory is that supported by the greatest amount of evidence. There can be no doubt, after the extensive researches conducted by numerous experimenters, that tubercle bacilli exist in dusts, being derived from the respiratory passages of consumptives during cough and expectoration. This has been found true in all the resorts of consumptives; the largest number of bacilli are found in the houses, rooms, and hospital wards occupied by tuberculous patients.

It is also true that tubercle bacilli occur in milk and sometimes in the solid foods, and that by their ingestion tuberculosis may be brought about. Ingestion tuberculosis is, however, most common in infants who are not exposed to any other mode of infection, and in them and adults similarly affected the lesions are chiefly centered about the alimentary canal, not in the pulmonary organs.

Aërogenic Tuberculosis of the Lung.—When the tubercle bacillus is inhaled into the lung, it is either arrested by the moist surfaces of the bronchioles or penetrates into the air-cells. The first change consists of a catarrhal inflammation of the alveolus, with desquamation and round-cell infiltration of the alveolar wall and an accumulation of round cells into the air-cell. The disease does not remain confined to the one air-cell, but begins to spread slowly in all directions, filling up the contiguous air-cells with inflammatory exudate, and infiltrating the interalveolar tissue until a small nodule—a miliary tubercle—is formed. The original focus continues to enlarge, and about it catarrhal pneumonia and infiltration progress. Such a tubercle, therefore, may be looked upon as an ever-increasing focus of inflam-

mation. From the air-cell originally infected, the disease in spreading extends to neighboring cells, then to infundibula, then to lobules. With its increase in size at the periphery there is a concomitant loss of vitality in the center, coagulation necrosis takes place, giant cells are formed, and eventually the entire cellular structure is lost, and there remains only a yellowish, granular, fragmented mass. The growth of the tubercle is accompanied by destruction of the capillary blood-vessels. It seems that the endothelial cells of the capillaries change their shape, obstruct the lumen of the vessels, prevent the circulation of blood through them, and ultimately undergo a hyaline degeneration and disappear.

The active growing part of the tubercle is at the periphery, where the new tissue is being invaded. The bacilli, which multiply in the tubercle, follow the same series of changes as the cells. At the periphery of the tubercle they are numerous and stain intensely; in the intermediate zone they

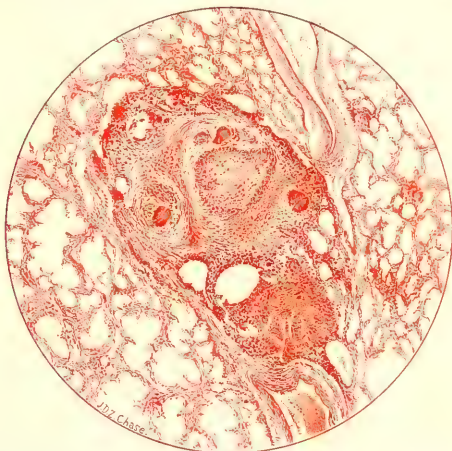


FIG. 278.—A miliary tubercle of the lung, consisting of two, probably three, submiliary tubercles. The coagulation necrosis of the center and the giant-cell formation are well shown. $\times 70$.

stain less well and are fewer in number; in the interior of the tubercle where the coagulation necrosis is far advanced they may be absent, or may be in the fragmented condition so constantly seen in the bacillus as it occurs in sputum.

It may be that the bacilli are carried from the periphery of the tubercle by currents of lymph, or they occasionally may be picked up by phagocytes and carried away into the lymph-spaces. At any rate, from one or the other cause the distribution of secondary tubercles begins soon after the formation of the primary tubercle, and continues through the lymphatics. At first in the near vicinity, later at some distance, and still later at remote parts of the organ and in the bronchial lymphatic glands, secondary miliary tubercles are formed.

Tuberculosis of the lungs due to inhalation ordinarily begins as a local process, most frequently situated in the apices.

The **hematogenic tuberculosis of the lung** develops in consequence of the distribution of tubercle bacilli through the venous circulation.

The lesions may follow the lodgement of a few bacilli absorbed through the lacteals or from the continued distribution of bacilli from some tuberculous area discharging into a blood-vessel. The latter condition, resulting in the formation of multiple miliary tubercles, is the more common.

The primitive tubercles result from the lodgement of bacilli in a capillary blood-vessel. The changes consist of alterations in the capillary endothelium, cessation of circulation, multiplication of the fixed connective-tissue cells, emigration of leukocytes, hyaline degeneration, coagulation necrosis, etc. The outcome is the formation in the interalveolar and alveolar tissue of discrete, prominent, gray miliary tubercles, about which the lung-tissue is hyperemic and more resistant than normal to the touch. The lung is not consolidated, however, though there may be more or less lobular pneumonia, but contains air and floats upon water. Cases with widespread miliary tuberculosis are generally fatal in a short time, as manifested by the small size and fresh condition of the miliary tubercles. If the individual live on the miliary tubercles increase in size, form caseous masses, and then give rise to secondary, consecutive infection through the lymphatics of the lung, exactly as in the *aërogenic* form.

In all forms of tuberculosis of the lungs the steady growth of the primitive tubercle causes it to trespass upon the alveolar tissue, where a catarrhal inflammation leads to consolidation of the tissue by accumulation of the exudate in the air-cells and the transformation of the lesion, whatever its origin, into a lobular bronchopneumonia.

In some cases it seems that the tubercle bacilli brought to the lung do not remain there, but are carried off by currents of lymph or by the activity of phagocytes to the bronchial lymphatic glands, and retained there. In how many such cases the bacillus is destroyed by the lymphatic cells no one can answer. When not destroyed the bacillus proceeds to grow and produce tubercles in the bronchial glands. It is furthermore difficult to determine how many cases of pulmonary tuberculosis originate from primary disease of the bronchial glands, but it seems to be true that when the glands are enlarged and softened as the result of tuberculosis with caseation, their rupture into a bronchus by ulceration, and the discharge of their infectious contents into the air-passages, can cause the aspiration of infectious material into the deeper parts of the lung and the sudden formation of an aspiration tuberculous bronchopneumonia. When the fatal issue comes, it has been preceded by so many changes in the lung that the original conditions are made out with difficulty.

Tubercles in a lung may progress rapidly in development or may be retarded by the vital resistance of the tissue. In the latter case organization progresses in the newer parts of the inflammatory zone—the most peripheral area—and the tubercle becomes encapsulated with more or less perfectly formed connective tissue, and may then remain unchanged for a long time, or be absorbed as the connective tissue contracts about it, or may calcify and remain thus for years. It is unknown for how long a time the tubercle bacilli enclosed in such encapsulated and calcified areas may retain their vitality. In some cases, however, they seem capable of remaining virulent for years, and it seems to be a rare but undoubted occurrence that when the

barrier preventing the progress of the tubercle is removed, the disease begins afresh and assumes particular virulence.

When the tubercles in the lung are closely approximated the intermediate tissue becomes indurated, not purely from tuberculous infiltration, but because the air-cells contiguous to the tubercles undergo a catarrhal inflam-



FIG. 279.—Tuberculosis of the lung. The upper third contains large cavities; the middle is in an advanced stage of caseation, while the lower lobe shows a more acute caseous pneumonia accompanied by the eruption of miliary, mostly peribronchial, tubercles.

mation and become occupied with masses of desquamated epithelium, small round cells, and fibrin. The result of the combined process is that considerable-sized consolidated areas of tissue in the lung upon section present a grayish appearance, with yellowish-white or yellowish-gray tubercles scattered in it.

The obstruction and obliteration of the bronchioles that constantly accompany tuberculosis of the lungs further damage the lung and complicate the morbid anatomy of the lesions by occasioning numerous scattered areas of atelectasis.

Approximated tubercles very commonly fuse together and form large necrotic, cheesy masses. The coagulation necrosis may even extend beyond the tubercle into the inflammatory infiltration. Sometimes the cheesy material is soft and purulent in appearance, more frequently it is crumbly. The escape of the contents of the tuberculous mass by way of the air-passages leaves a ragged hole—a cavity or vomica—in the lung-tissue. The cavities have rough, irregular walls, chiefly consisting of cheesy material, which by continually crumbling away increases the size of the cavity. As a tuberculous node grows and extends into fresh tissue by the formation of



FIG. 280.—Caseous pneumonia, showing the advanced and early stages of this form of tuberculous invasion. $\times 135$.

outlying tubercles, its necrotic center is thus often crumbling away and increasing the size of the formed cavity. Blood-vessels or bronchioles may cross the cavity from side to side, or may project into it. Sometimes bronchial dilatation leads to a further increase of size. It may happen that a bronchus ends at one side to begin again at the other, the intermediate portion being totally destroyed. When such a condition is present, the mucous or other secretion formed in the inner portion of the eroded bronchus must be emptied into the cavity before it can escape from the tubes. On the other hand, when the bronchitis that is always a symptom of pulmonary tuberculosis causes the secretion of mucopus in the larger tubes, it may be aspirated into the cavity during inspiration and be expelled from it with difficulty subsequently. The walls of the cavities frequently contain capillaries whose unsupported walls are injured during cough, etc., and which ooze or bleed subsequently. Sometimes the tuberculous process ulcerates

through larger blood-vessels and causes extensive—even fatal—hemorrhages. Thus, from a variety of causes, the cavity is filled with a mass of matter consisting of all kinds of tissue-remnants and inflammatory and secretory fluids, and becomes just the nidus for the development of any bacteria, saprophytic or parasitic, that may be carried in with the inspired air. Some cavities progress in size for a considerable time, apparently without any external infection, and give upon bacteriologic examination pure cultures of tubercle bacilli. The majority, however, become infected, and the result of the growth of the *Staphylococcus pyogenes aureus* and *albus*, the *Streptococcus pyogenes*, the *Micrococcus tetragenus*, *Bacillus mucosus capsulatus*, the pneumococcus, and others, added to the already destructive tuberculous process, will make the disease locally much more destructive by setting up acute inflammatory processes, and much more malignant, constitutionally, by exciting hectic fever, etc.

The cavity is, furthermore, a source of perpetual auto-infection. From its crumbling walls tubercle bacilli are being detached, and, together with the caseous matter containing them, discharged into the air-passages. Thus, infectious matter is constantly placed where it can be drawn into the alveolar structure of the lung during inspiration, to produce tuberculous bronchopneumonia, and during expiration be forced through the bronchi, trachea, larynx, and mouth, in any or all of which parts the bacilli may fall upon abraded surfaces and produce local tuberculous lesions. In its passage through the mouth the sputum may be swallowed and an infection of the intestine set up.

A still further possibility is that the tuberculous node in its softening will erode a vein and discharge its contents into the systemic circulation, to all parts of which tubercle bacilli will be conveyed and set up a consequent *acute general miliary tuberculosis*.

So long as a tubercle is without communication with the veins and bronchial tubes by ulceration the spread of the disease is limited to slow travel along the lymphatics. Given an ulcerated and discharging tuberculous cavity, however, and the infection may become widely spread in a very short time.

As tuberculosis of the lung is almost always accompanied by catarrhal pneumonia, so the catarrhal pneumonia and discharge of caseous material from the tubercles into the bronchi cause a more or less severe bronchitis. In the beginning the bronchitis is purely catarrhal unless the tuberculosis be primarily bronchial; but later, after cavity formation has occurred, the bronchial tubes rarely escape infection and tuberculous ulceration. The conditions that infect the bronchi also apply to the larynx.

As may be imagined, so destructive a process cannot go on in the lung without damaging the pleura, which becomes the seat of chronic pleurisy with thickening and with adhesions. In the cases with cavity formation the communication of a cavity with the pleura leads to pneumothorax. Empyema is also of common occurrence.

The morbid anatomy of pulmonary tuberculosis is highly characteristic and varies with the form of the disease.

In the **acute miliary tuberculosis** of the lung the pulmonary tissue is found studded everywhere with minute gray tubercles, pretty evenly distributed throughout the organ. The intervening tissue is hyperemic and may be partly consolidated.

Caseous tuberculous bronchopneumonia and **pneumonia** is the fatal form of acute pulmonary tuberculosis described by clinicians as *phthisis florida* (galloping consumption). In nearly all cases a primary focus exists, from which the disease has spread. This is usually situated in an upper lobe, and may have advanced to cavity formation. The pneumonic process occurs in multiple areas, or it may affect part of a lobe, a whole lobe, or a whole lung. The tissue is consolidated, airless, anemic, pale in appearance, of a grayish or grayish-yellow color, and sometimes friable and cheesy in consistence. Close inspection may disclose the presence of small miliary tubercles here and there in groups. The lesion is not rarely mistaken for the gray hepatisation of croupous pneumonia. The pleuræ are slightly thickened, or in rapid cases covered with a fibrinous exudate as in pneumonia.

Caseofibroid tuberculosis is the ordinary form of pulmonary phthisis. The invasion usually begins at the apices, where the disease will be found in

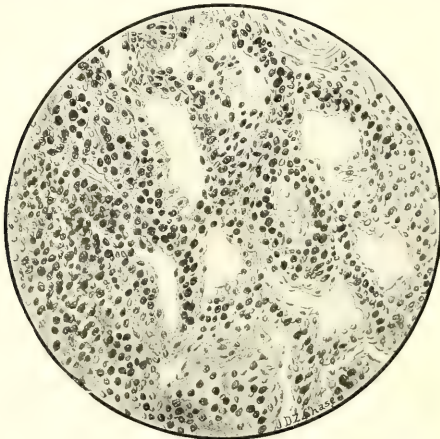


FIG. 281.—Caseous pneumonia; early stage.

all its aspects of fresh miliary tubercles, agminated tubercles forming small consolidated areas, cheesy areas from combined tubercular and pneumonic processes, softened cheesy areas, cavities large or small, etc. Here and there distinct fibroid indurations are found, partly due to attempted organization so common in chronic tubercles, partly to interstitial pneumonia. Secondary inspiration tubercles and scattered lymphogenic metastatic tubercles occur in the more normal parts of the lung. When the disease is so far advanced as to have invaded the whole lung the pleura will be much thickened, its internal extensions thickened and prominent, the edges of the lung and the newer parts may be atelectatic, and the older parts, especially the upper lobes, may be riddled with cavities. Pleuritic adhesions are common.

Fibroid tuberculosis is the most chronic form. It seems to occur only in persons with great vital resistance or unusual immunity to the disease. The lesions illustrate the predominance of the regenerative ability of the

individual over the spread of the disease. The tubercles and tuberculous areas are continually being isolated, encapsulated, and constricted by a profuse hyperplasia of connective tissue, which not only checks the advance of the disease considerably, but unfortunately also compromises the integrity of the remaining breathing space, and deforms the lung. The disease may originate from a tuberculous pleuritis or from the ordinary apical tuberculosis. In the course of time the amount of cirrhosis may be so great that it is impossible to recognize the lesion as tuberculosis. Ordinarily, however, a few tubercles occur here and there or an old cavity may be found. The cirrhosis not only causes the lung to become indurated, but also reduces its size. In this form of tuberculosis bronchial dilatations are quite frequent. Old encapsulated calcareous tubercles are also common.

When, as not infrequently happens, the pulmonary and costal pleuræ unite by firm adhesions, the subsequent contraction of the connective-tissue bands within the lung causes marked deformity of the chest.

The fibroid tuberculosis is usually common to both lungs, but is usually more advanced in the one than in the other. The uninvaded lung-tissue is usually emphysematous.

Syphilis.—Syphilis of the lung is a rare affection, and one that has fewer characteristics than might be expected. The chief forms are the gumma and the "white pneumonia."

Gumma of the lung is extremely rare. It appears as an inflammatory node consisting of a cheesy necrotic central zone of varying size and a narrow peripheral zone of translucent connective tissue circumscribing the whole. The gumma resembles that of other organs. It varies in size from a pea to a large egg, and is more common near the root of the lung than elsewhere. The lesion is with much difficulty differentiated from the single caseous tuberculous masses frequently seen in the lung. When subjected to microscopic study the differentiation of the two lesions may depend entirely upon the presence of tubercle bacilli.

The gumma runs the ordinary course of increase, coagulation necrosis, and cicatrization, and, by rupture into a bronchus, may lead to the formation of a cavity. The contents frequently become inspissated and calcified. Subsequent to the absorption of the gumma a stellate scar appears upon the pleural surface. Deep puckers and radiating scars upon the pleura are, however, frequent after abscess, infarction, gangrene, and other pulmonary diseases, and are probably less characteristic of syphilis than elsewhere.

White Pneumonia of the Fetus.—This congenital form of the disease consists of a hyperplasia of the interalveolar connective tissue in larger or smaller areas of the pulmonary tissue, and a resulting consolidation of the organ and diminution of air-capacity. A whole lung may be affected. Even if the child be born alive and breathe, the diseased part of the lung is still not inflated, and upon microscopic examination the tissue has the appearance of atelectasis with an added proliferation and desquamation of the alveolar epithelium.

In other parts the lung may contain dense, firm areas in which, in addition to the connective tissue, areas of round-cell infiltration are present.

To the naked eye the tissue appears grayish white, firm, heavy, and anemic. The anemia and the unpigmented condition of the lung give it the name of white pneumonia.

Interstitial fibroid pneumonia, beginning near the root of the lung and

extending along the air-tubes, is described by Virchow as syphilitic in its origin. In some cases the occurrence of the condition with gumma formation and syphilitic history seems conclusive of its origin.

Actinomycosis.—Pulmonary actinomycosis in man may be primary or secondary to the oral, pharyngeal, and esophageal forms, resulting from the entrance of infectious pus into and the distribution of pus throughout the system of air-tubes, or it may be metastatic. The disease appears as a chronic bronchitis, with a fetid discharge of mucopus in which the actinomycelial "grains" are present. This form of the disease, from the distribution of the infection with the inspired air, may cause a disseminated or miliary form of the disease, bearing a partial resemblance to miliary tuberculosis. Typical cases of this form are very rare. The freshly developed nodules are gray or gray red in color, but are apt to have yellowish centers from the fatty metamorphosis that takes place within them. In the immediate neighborhood of the fungus the pus is creamy white. As the disease spreads and the nodules become more numerous, neighboring nodules may fuse and form larger nodes surrounded by grayish bronchopneumonic areas. Pressure upon such areas sometimes causes the fungous granules to appear. Microscopic examination of the contents of the softened areas shows pus-cells, fat-cells, fat-drops, broken-down blood-corpuscles, etc. The cavities formed by the softening may be large enough to be diagnosticated during life.

Other cases, or sometimes more advanced cases, manifest an indurating character, and around the nodules dense fibrillar connective tissue forms, encapsulating them more or less completely. The connective tissue is not limited to the capsule about the actinomycotic focus, but becomes more diffuse and invades the neighboring interalveolar tissue. The induration progresses hand and hand with an exudative catarrhal pneumonia.

The disease does not usually tend toward recovery, but, like the majority of the specific granulomas, is progressively destructive.

In the course of time much of the lung affected may be changed to an indurated, shrunken, nodular mass of tissue with rather numerous suppurating cavities and sinuses, and many small or large actinomycotic nodules.

The most conspicuous induration is found at the oldest part; the most obvious suppuration in the freshly invaded areas.

Pleuritic adhesion and union of the pleural surfaces which follow the extension of the inflammation to the pleura are followed by the progress of the disease through the thoracic walls to the pectoral and other muscles and to the skin, or through the diaphragm to the peritoneal surfaces and abdominal organs.

Instances of ray-fungous (streptotricheal) infection of the lungs, resembling tuberculosis both clinically and anatomically, have been described by Flexner and others.

Glanders.—This affection is extremely rare in man, and, like most of the glanders-lesions, is usually seen in those coming in contact with animals suffering from the disease.

The pulmonary form is characterized by the formation of cellular nodules of a yellowish-white color, the size of millet seeds and small peas. Aberrations from this type may be observed in the form of more or less extensive pneumonic areas, purulent and hemorrhagic infiltrations.

The pathologic diagnosis must be made by the demonstration of the *Bacillus mallei* and the results of inoculations into guinea-pigs. In the absence of a definite clinical history the lesions may be perplexing. The essentially suppurative character of the lesions is suggestive.

Tumors.—**Primary tumors of the lung** are of rare occurrence. Of the connective-tissue tumors, numerous cases of *osteoma* are on record. The condition seems to occur through the ossification of hyperplastic interstitial connective tissue. Ribbert describes ossification of caseous foci. A few cases present themselves in the form of isolated nodular new growths. One must be careful to differentiate between calcareous concretions occurring in old tuberculous and other areas and true bony formations.

Chondroma is also rare, sometimes having its origin in the cartilages of the bronchi or possibly in included embryonal elements. More frequently chondromas are metastatic, the embolic having their origin in primary chon-



FIG. 282.—Metastatic sarcoma of the lung; a sarcoma embolus in one of the small veins. $\times 135$.

droma of the extremities of the body. The tumors are circumscribed and present the usual characteristics. Osteochondroma, osteosarcoma, fibroma, and lipoma are also described, but are of rare occurrence in the lung.

Primary *sarcoma* of the lung is rare. It is usually of the small round-cell variety, and probably originates from the lymph-follicles.

Endothelioma of the pleura very commonly invades the lung, and has been mistaken for both primary sarcoma and carcinoma.

Primary *carcinoma* of the lung is even more rare, and most frequently has its starting point in the bronchi from the mucous glands. The subject has been studied by Langhans, who found the disease to be centered chiefly in one bronchus, from which it extended in the peribronchial tissues and then to the infundibular and alveolar structures. In the larger nodes caseation is apt to progress. To the naked eye the disease closely resembles tuberculosis. In the surroundings of the primary carcinoma mass secondary

peribronchial and interlobular nodules and solid injections of the subpleural lymphatic vessels with carcinoma-cells are observed.

The bronchial and tracheal lymphatic glands are early involved.

It also seems possible that primary carcinoma of the lung may originate from the squamous epithelium of the air-cells, but this is not yet satisfactorily demonstrated in spite of occasional cases that have been reported.

The primary carcinoma nodes seen in the bronchi form uneven nodular papillary growths. Portions from the primary growth sometimes break off and are inspired to deeper parts of the bronchial tubes, producing secondary masses in the bronchioles and air-cells, not only of the same bronchus, but also of other bronchi. In this way the distribution is both through the air-tubes and through the lymphatic system.

Sometimes the neoplasm forms large solitary medullary nodes which it is impossible to recognize as of bronchial or alveolar origin. The tumor spreads peripherally, affecting air-cell after air-cell and stuffing the lymphatics with cell-nests in its progress.

Secondary tumors of the lung are numerous and of various kinds. The metastatic chondromas have already received mention. With rare



FIG. 283.—Section of the lung in secondary carcinoma, showing a carcinoma embolus in a vein. $\times 180$.

exception the secondary tumors are all malignant. They occur chiefly by hematogenous distribution, the tumor-cells being retained in some of the finer capillary structures of the lung, and there multiplying so as to produce rounded nodes whose macroscopic and microscopic essentials are very much like those of the parent tumor. The nodes increase by peripheral infiltration.

The secondary tumors, both sarcoma and carcinoma, are recognized as such by their multiple occurrence, circumscribed contour, and by the existence of a primary focus. There is an interesting form of secondary carcinoma of the lung in which there is a more or less well-marked diffuse infiltration of the lymphatic networks, both subpleural and pulmonary.

Parasites of the Lung.—The most important animal parasite of the

lung is the *Tænia echinococcus*; the *Cysticercus cellulosæ*, *Strongylus longivaginatus*, monas, and cercomonas, coccidia and psorosperms, all being mentioned in works upon parasitology, but being too rare to merit separate consideration here.

The echinococcus-cysts may be either primary or secondary. When secondary the primary seat of disease is usually in the liver, the disease spreading to the lung by rupture through the diaphragm. Sometimes, but rarely, the infection takes place through the hepatic vein, inferior vena cava, and right heart.

The cysts sometimes occur in the upper lobes, but are much more common in the lower lobe, and especially on the right side. The cysts vary in size, sometimes attaining the size of a man's head. When large they are naturally associated with distention of the chest and displacement of the thoracic organs. Downward displacement of the diaphragm is usual. Curvature of the spine sometimes occurs in young persons.

The cyst-contents may be absorbed or may suppurate, the last small remnant calcifying. The most common termination is by rupture during cough or exertion, the contents being discharged into the pleural cavity or into a bronchus, to be expectorated together with some blood. Occasionally they rupture into the abdominal cavity.

Rare cases have been described by Scheuthauer, Virchow, and others, in which the cysts occupied branches of the pulmonary artery, lymphatic vessels, and the veins.

The cysts may be single or multiple (multilocular). They have the usual characteristic of the echinococcus-cysts, and may be recognized by the laminated walls and the presence of hooklets in the contained fluid.

Sometimes, when the cysts rupture, fragments of their walls enter the expectoration, rendering the clinical diagnosis more easy. Such fragments have an appearance resembling milk-glass, and are of a bluish-white color and cartilaginous consistence. Larger pieces have a tendency to curl up, the free edges inward. The expectorated matter may also contain hooklets, the discovery of which during life is pathognomonic.

The lung-fluke, or *Paragonimus Westermanii* (also known as *Distomum Westermanii*), is a rare but important parasite. It occurs for the most part in tropical countries, and in Asia and Africa in particular. A few instances have been observed in this country in cat, dog, and swine. The greater number of cases have occurred in the lower animals—the tiger, cat, dog, and hog—but the disease “paragonimiasis,” as Stiles¹ calls it, also occurs in man, producing an affection known as parasitic hemoptysis, endemic hemoptysis, lung-fluke disease, gregarinosis pulmonalis, etc. Of 66 cases collected by Stiles, 58 were in men and 8 in women. The disease runs a chronic course, but the greater number of cases recover. The worms are flukes (trematode worms), and to the naked eye have much the size and shape of small almonds. The morbid anatomy of the affection varies according to the position and operation of the parasites. When in the bronchial tubes, they are found adhering to the mucous membrane by suckers at the anterior portion of the body. It seems that the parasites do not remain localized, but burrow through the pulmonary tissue from place to place, causing the formation of cavities the size of a filbert, with communications between them, and into neighboring bronchial tubes. “Some communicate directly

¹ *Proc. Phila. Path. Soc.*, xxviii., 506, 1900.

with a bronchus, the lumen of the latter and the burrow forming one cavity, while the bronchus presents the appearance of having a sac-like dilatation on one side. Such cavities are probably formed by the exit from a burrow to the bronchus becoming enlarged, and finally the partition between adjacent burrows breaking down and one cavity being formed. Each cavity is surrounded by a ring of irregular induration, extending much further into the parenchyma of the lung in some directions than in others. The adjacent bronchi are congested and more or less inflamed. So, also, the circumjacent lung-tissue is congested. The cavities contain broken-down lung-tissue, hematoidin, ova, débris, or dead specimens of the parasite. In one case twenty distomas were found. The contents of these cavities, mixed with the mucous secretions of the bronchi, form the characteristic sputa." The article by Katsurada¹ contains a good description of the pathologic changes in infected human lungs.

The adult parasite infests man. The ova are supposed to develop partly in water, partly in some mollusk. Man is probably infected through drinking-water.

THE PLEURA.

There seem to be but few primary affections of the pleuræ. This does not mean, however, that the pleuræ are rarely diseased; for, on the contrary, the delicate nature of the structure, and its intimate relation to the lung, chest-wall, and diaphragm, make its secondary involvement in morbid processes of neighboring organs very frequent.

Not only are the pleuræ subject to extension of disease by continuity and contiguity of tissue, but they are also involved in certain systemic morbid processes, notably the infectious diseases and the dropsies, in the former of which one frequently encounters small intrapleural or subpleural pectechiæ or larger ecchymoses, and in the latter collections of watery fluid.

Blood in the Pleural Cavity.—Petechial hemorrhages into the pleura are not infrequent in the infectious diseases. Large collections of blood in the pleural cavity—hemothorax—are rare. They may depend upon traumatism, as, for example, a fractured rib, rupture of aneurysms, the *morbus maculosus Werthofii*, scurvy, or to destructive ulcerative and neoplastic diseases of the pleura and neighboring tissues, as carcinoma, sarcoma, and tubercle. The largest collections of blood enter the pleural cavities from ruptured aneurysms. Blood escaping into the pleural cavity coagulates slowly, and is eventually gradually absorbed. In the process of absorption, however, the pleural cavity may be obliterated by fibrous proliferation from the surfaces of the pleura. The obliteration of the part of the pleural cavity in which the absorbed coagulum was situated is analogous to the obliteration of the lumen of a blood-vessel in which a thrombus has formed.

If the intrapleural hemorrhage by the entrance of air becomes contaminated by bacteria, the coagulum putrefies readily and suppuration or gangrene may follow.

Chyle in the Pleural Cavity.—Chylothorax is an extremely rare affection characterized by the presence of a milk-like fluid in the pleural cavity. Upon standing, a supernatant fatty, cream-like layer may form upon the liquid. The condition is only known to occur in cases of injury to the thoracic duct.

¹ Ziegler's *Beiträge*, xxviii., 506, 1900.

Serum in the pleural cavity is common. It may occur in consequence of heart or kidney disease—hydrothorax—or may result from inflammation of the pleura.

Hydrothorax is the term used to indicate a collection of serum occurring independently of inflammation in the pleural cavity. Such an accumulation is generally bilateral, but may be unilateral, occurring generally first and sometimes only in the pleural cavity of the side upon which the patient is accustomed to lie. As Eichhorst points out, most persons lie most comfortably upon the right side, hence the hydrothorax most commonly begins on that side. Other observers believe that the occurrence of the hydrothorax upon the right side depends upon the fact that the distended right auricle of the heart interferes with the exit of blood from the *vena azygos*.

Hydrothorax usually follows disease of the circulatory system, sometimes disease of the respiratory system. It is also common in nephritis, the cachexia of cancer, and various conditions of bodily weakness and anemia. It may occur during the death-agony, and it is probable that many of the collections of fluid found in the pleural cavities after death had no existence until the last moments of life. At this point it should be mentioned that considerable accumulations of fluid are found in the pleural cavities of drowned persons, from the passage of water from the lungs to the pleural cavities by exosmosis after death. In edema of the lungs the fluid in the pleural cavity increases after death, by the percolation of the fluid through the wall of the lung.

The fluid in hydrothorax is clear and amber-colored (may be slightly blood-stained when the patient has had pulmonary congestion before death), and is, as a rule, free from floating flocculi of fibrin. The surfaces of the pleura containing it do not vary from the normal.

Sometimes the fluid contains cholesterin-crystals. The reaction is alkaline; the specific gravity 1009–1012, sometimes higher. The amount of albumin in the fluid varies from 27.82 (Hoppe-Seyler) to 49.77 (Scherer) in 1000 parts of liquid. The quantity of fluid may be very great—as much as 5 quarts—5 liters—and may seriously embarrass breathing, even causing death from suffocation.

Usually the fluid is free to move, and gravitates according to the position of the patient; but if there have been previous pleuritic inflammations with the formation of adhesions, the fluid may collect in whatever open spaces remain, forming, according to the existing circumstances, *circumscribed*, *sacculated*, or *multilocular hydrothorax*, in which the fluid is so confined as to be unable to change its place according to the movements of the body.

When the accumulation of fluid has existed in the chest for a long time, the pleura, both pulmonary and costal, becomes thickened, whitish, glazed, and shining.

When the fluid within the pleural cavity has a specific gravity greater than 1015, contains many fibrinous flocculi, or is clouded in appearance, one should suspect the case to be of inflammatory instead of dropsical origin.

Pleuritis, or inflammation of the pleura, presents a varied picture according to the circumstances under which it occurs. In all cases of pneumonia, and in all pulmonary subpleural affections—tubercle, neo-

plasms, infarctions, etc.—local pleurisy affecting the membrane over and contiguous to the diseased area is present. The pleurisy in these cases is of an exudative nature, characterized by the presence of a fibrinous deposit upon the surface. This deposit consists either of a layer of fibrin forming a pseudomembrane, or of an irregular deposition of whitish flakes of semi-adhesive fibrin distributed over a dulled, thickened, and sometimes hyperemic pleural surface.

Pleurisy with fibrinous exudate of this kind sometimes, but rarely, occurs as a primary affection in individuals of depressed vitality. Under these conditions it affects the whole pleural surface.

Except the distinctly localized forms, few cases of pleurisy remain fibrinous; nearly all are sooner or later accompanied by a serous exudate. The ordinary form of pleurisy with effusion might be described as sero-fibrinous, the exudate consisting chiefly of serum, but containing also considerable fibrin floating as flocculi in the liquid or distributed upon the pleural surfaces in ragged shreds, more or less widespread smears, or almost complete membranous layers upon the entire pleural surface. When the pleuræ themselves are so coated the dependent parts contain curds of white or creamy appearance and buttery consistency. The serum is of a yellowish-green color, and may be clear or may contain enough fibrin to make it turbid. It varies in quantity from a few cubic centimeters to 5 liters—5 quarts. According to the presence or absence of red blood-corpuscles, etc., the fluid varies from a straw color to a reddish brown.

There are few organized bodies in the exudate. Upon microscopic study one finds a few leukocytes, a few erythrocytes, some distorted endothelial cells, and shreds of fibrin.

The specific gravity of the fluid is almost invariably above 1025. It coagulates readily when heat is applied, and when removed from the body not infrequently coagulates spontaneously. In composition the inflammatory pleuritic exudate differs from the effusion of hydrothorax in being more albuminous and in containing more uric acid, cholesterolin, and sugars. The composition is more nearly the same as that of blood-serum.

When the inflamed surfaces of the pleura have not been made adherent to each other by previous disease, the pleuritic effusion occupies the lowest part of the pleural cavity and changes its position to accommodate itself to the upright or prone position of the patient. The lung floats up upon the fluid, but when there is a large exudation the lower part of the lung is compressed, airless, tough, and gray, gray black, or brownish in color. The upper lobe of the lung may be inflated. The effusion is, as a rule, unilateral. The heart is more displaced when the effusion is on the left side than when on the right. The diaphragm is depressed and the intercostal spaces bulge. The great vessels of the thorax may be compressed. In right-sided pleuritis the liver is pushed down into the abdominal cavity.

The absorption of an exudate may take place slowly or rapidly. It makes little difference in the subsequent course of events whether the fluid be removed by absorption or by aspiration. After the disappearance of the serum the fibrin remains, and is usually succeeded by the outwandering of leukocytes, the proliferation of the cells of the pleura, and the formation of a permanent white or grayish patch of connective tissue corresponding to the diseased area. Larger and extensive proliferations are succeeded by

white callous thickenings of the pleura, and when, as often happens, corresponding portions of the pulmonary and costal pleuræ are simultaneously affected, subsequent fibrous union of the two surfaces occurs. At first the fibrous union is intimate; but if the lung be free elsewhere and moves with the respiratory efforts, the adhesions are constantly drawn upon, the new tissue is compelled to yield and becomes more and more stretched, until, instead of the original intimate union, the opposed portions become connected by fibrous bands and cords varying in thickness and number according to the extent of diseased tissue. As the age of these cords advances they become very tough and strong, and may resemble the chordæ tendineæ of the heart. Extensive adhesions more or less completely obliterate the pleural cavity. If an exudative pleuritis is chronic because of chronic disease of the lung, and if at the same time the lung is not free to move, extensive inflammation may totally obliterate the pleural cavity. It is not uncommon to find union between lobes of the lung. The most frequent adhesions occur at the apices posteriorly. They may bind the lung to the costal pleura and to the diaphragm.

When it happens that the absorption of the serum is delayed, so that the inflamed surfaces are kept separated from one another for a long time, great thickening of the pleura may occur, surround the lung like a callous rind, and send prolongations into the interlobular septa. By the contraction of such an encapsulating mass of tissue the lung may be deformed, its borders being rounded, and its air-capacity greatly diminished.

Suppurative pleuritis (*pus in the pleural cavity; empyema*) is sometimes a primary affection, especially in children. Usually it depends upon previous disease of neighboring organs. Sometimes it comes on insidiously in the serous pleurisy of healthy individuals, especially in the convalescence of pneumonia. It is probably most often due to the rupture of tuberculous cavities of the lung, perforation of the diaphragm in abscess of the liver, perforation of cancerous and other ulcers of the esophagus and stomach, and the escape of infectious matter into the pleural cavity. It may also be part of general septic infection, and sometimes follows traumatism with the entrance of bacteria of suppuration into the pleural cavity. Gangrenous affections in the neighborhood of the pleura may cause it.

Sometimes a serous or a fibrinous pleurisy may become secondarily suppurative.

The micro-organisms found in the pus vary considerably with the time of life at which the empyema occurs. Thus, in children the pneumococcus is most frequently met, while in adults it is the streptococcus. In adults the number of tuberculous empyemas is nearly twice as great as in children. The following table from Netter will amply explain the differences:

	Children.	Adults.
Pneumococcus	53.6	17.3
Pneumococcus and streptococcus	3.6	2.5
Saprophytic organisms	10.7	
Staphylococci		1.2
Tuberculous cases	14.3	25.0
Streptococci	17.6	53.0

The nature of the pus will depend upon the cause of the disease. At times it is yellow and creamy; at others it may be curdy and flaky; at still others it is foul-smelling, discolored, and decomposed, as in gangrenous diseases.

The pus may at times be absorbed when the virulence of the infection has been overcome. It is possible for the pus to erode the pulmonary tissue, rupture through the pleura, and evacuate through a bronchus. Such a termination is, however, unfortunate, as it produces a pyopneumothorax (see below).

The pus may also penetrate the costal pleura, dissect its way between the ribs, and point externally as an abscess. Such "pointing" generally occurs near the sternum, between the lower costal cartilages. Empyemas may also rupture into the esophagus, stomach, peritoneum, or pericardium. Osler speaks of remarkable cases which extend down the spine and simulate psoas-abscess.

An empyema may also extend to the neighboring tissue, producing disease of the mediastinum, pericardium, peritoneum, and retroperitoneal tissue. An empyema of one side may, by passage of the inflammation through the mediastinum, produce empyema of the other side, though empyema is generally a unilateral affection.

The recovery of empyema after natural or surgical evacuation is slow, for the pleuræ continue to form pus upon their surfaces for some months.

When evacuated into an aspirating-bottle the pus frequently sediments, leaving an upper clear serous layer and a lower stratum of pus-cells. It is the same in the chest as in the aspirating-bottle, and when at autopsy the pleural cavity containing pus is opened, the pus-corpuscles are generally found in the lower stratum of the fluid. The pleuræ are generally coated with fibrin, and sometimes exhibit ulcerations and erosions. The quantity of pus varies, and, as in the serous effusions, the quantity may be great.

After empyema it is unlikely that the integrity of the pleuræ is ever reinstated. The protracted course of the disease and the destructive changes accompanying it predispose to the formation of pleural thickening, which may be succeeded by deformity of the chest, as described.

Air in the Pleural Cavity (*Pneumothorax*; *Pyopneumothorax*; *Hydropneumothorax*).—Air gains entrance into the pleural cavity in a variety of ways. Most commonly it depends upon the rupture of the wall of a tuberculous cavity. It may occur in consequence of the rupture of a normal lung from violent straining efforts, but does not give rise to the usual complications under these circumstances; a single pleural inflammation is all that one would expect to find as the result of the laceration. It may also follow rupture of a diseased pleura.

Occasionally it happens that air gains entrance to the pleural cavity as the result of such traumatisms as perforative wounds of the chest, fracture of the ribs, and even punctures made to explore the pleural cavity. In very rare cases air may enter from unusual sources, as when there is malignant disease of the esophagus with rupture into the pleura, or perforation of the diaphragm in cases of malignant disease of abdominal viscera.

The most common cause is the rupture of a tuberculous lung during cough. The fact that gas production may be due to the presence of *B. aërogenes capsulatus* should not be neglected.

Air is not dangerous in itself, but in nearly all of the conditions by which it enters the pleural cavity bacteria are carried in with it, so that few of the consecutive pleurisies are simple, nearly all becoming suppurative.

The entrance of air into the pleural cavity is called **pneumothorax**. It is uncommon as an uncomplicated condition. Ordinarily the damage done

to the pleura is sufficient to cause an outpouring of serum and form a **hydro-pneumothorax**. If no further changes occur, the air in the simple pneumothorax and the air and the fluid of the hydrothorax may be absorbed, leaving no further changes than one would find in simple pleurisy—thickening of the pleura, adhesions, etc.

When, however, micro-organisms of suppuration enter with the air, or get in subsequently to the pneumothorax, an empyema is added—**pyopneumothorax**.

The rupture of tuberculous cavities always leads to pyopneumothorax, not only because of the presence of tubercle bacilli, but also because from the ruptured cavity or bronchial dilatation pyogenic bacteria accidentally present also enter. In tuberculosis the fistula does not tend to heal, and the condition is permanent unless an accidental deposit of fibrin temporarily plugs the hole, or an adhesion forms above it, both changes being quite unusual.

The perforations are usually situated in the upper lobe, and close examination will often reveal the fistula as a small opening (pin or quill size) at the bottom of a small concavity upon the pleural surface. The opening may be circular, slit-like, or irregular.

Weil divides the cases of pneumothorax into three chief forms:

Open pneumothorax, in which the air is free to pass in and out.

Ventilated pneumothorax, in which air can enter during inspiration, but cannot escape during expiration. The entrance of air ceases when the air-pressure in the pleural cavity has a maximum pressure equal to that in the lung.

Closed pneumothorax, in which the fistula has closed.

The classification is not supposed to preclude a ventilated pneumothorax from becoming a closed one, or the possibility of any other change taking place.

The pyopneumothorax remains unchanged so long as the fistulous opening allows air to pass from the lung or exterior into the pleural cavity. As soon as the opening closes in any way the condition is changed, and the absorption of the air transforms the pneumothorax into an empyema with ordinary characteristics and terminations.

Tuberculosis.—Tuberculosis of the pleura deserves attention apart from that already given it under the description of tuberculosis of the lungs, because sometimes it is primary and depends upon the lodgement of tubercle bacilli brought to the pleura by the circulating blood. The condition seems to be more common in the lower animals than in man, and, because of the clusters of rounded, translucent masses of granulation-tissue formed by the tuberculous tissue, is called "pearl disease" in cattle. The same condition is seen in man, but is rare.

Tuberculosis of the pleura is usually secondary to tuberculosis of the lung. It may be secondary to tuberculosis of the ribs or of the bronchial lymph-glands or other organs or tissues in the neighborhood. Cases have been reported that originated from caries of the spine.

The ordinary pleuritis of pulmonary tuberculosis is a fibrinous agglutinative pleuritis which especially seals the adjacent surfaces together. When, however, tubercle bacilli escape into the pleura, they form small gray miliary tubercles in the tissue of the membrane along and on the lymphatic vessels. At the same time that this change is in progress a serofibrinous or even hemorrhagic pleuritis may affect other portions of the membrane. Very

often empyema results from the presence of tubercle bacilli, though in these cases it is difficult to make sure that it is from the tubercle bacillus alone.

The fibrous adhesions resulting from subpleural tuberculosis very often contain large numbers of tubercles in the granulation-tissue.

To the miliary or conglomerate tubercles thus formed upon the pleura must be added pleuritis in all its forms. It may be that the tubercle eruption is accompanied by a simple serofibrinous pleuritis; it may be that empyema forms; or it may be that the rupture of pulmonary tissue that allowed the tubercle bacilli to escape from the lung into the pleural cavity also allowed the escape of air and the formation of pneumothorax with all its varied consequences.

Other specific inflammatory affections of the pleura, such as glanders,



FIG. 284.—Endothelioma of the pleura. $\times 145$.

syphilis, lepra, actinomycosis, etc., occur, but have no peculiarities requiring description separate from those devoted to the general considerations of the diseases.

Tumors.—Primary tumors of the pleura are rare. Among those reported are endothelioma, fibroma, sarcoma, angioma, lipoma, and osteoma. These tumors are all sufficiently characteristic to need no separate description here, except the *endothelioma*.

Endothelioma of the pleura is a rare malignant neoplastic disease characterized by the presence of multiple flattened coalescent nodes, sometimes connected by bands. The nodes are whitish in color. More rarely the tumor occurs in the form of large soft solitary tumors, in whose surroundings the pleura is thickened. Usually there is associated serous or

hemorrhagic pleurisy. The growth may spread rapidly and invade the lung and lymph-nodes, or it may remain solitary and grow slowly.

The tumor is characterized histologically by the formation of cell-nests similar to those of carcinoma, situated in dense connective tissue. The spaces, no doubt, represent lymph-spaces in whose distribution the endothelium has become proliferated as one leaves the older parts of the tumor and examines the younger infiltrating parts of the growth, the cells becoming more embryonal in type may so differ from endothelium as to make the growth resemble lymphosarcoma. The tumor is malignant.

Secondary tumors frequently involve the pleura either by continuity of tissue or by metastasis. Probably the most frequent are those following carcinoma of the mamma, thyroid, and esophagus. The tumors develop in the course of the lymphatics, and generally occur in the form of numerous disseminated nodules.

The presence of tumors in the pleura usually excites pleuritis, either serofibrinous, purulent, or hemorrhagic in type.

Parasitic diseases of the pleura are rare. Echinococcus is mentioned as following primary echinococcus of the lung.

THE MEDIASTINUM.

The diseases of the mediastinum are few in number and mostly of secondary origin. The enlargement of the lymphatic glands at the roots of the lung in its inflammatory diseases has already been mentioned. It not only occurs in pulmonary diseases, but also in measles and other specific diseases, and at times depends upon primary tuberculosis.

The formation of mediastinal abscesses by the extension of inflammation from the pleura to the cellular tissue of the mediastinum, in cases of empyema, has likewise been discussed.

Independent primary mediastinitis affecting the cellular areolar tissue of the mediastinum is uncommon. It may be anterior, median, or posterior, and is sometimes acute and suppurative, sometimes chronic and productive. The affection is generally either of traumatic or rheumatic origin.

Mediastinal emphysema also occurs at times in consequence of traumatism or of ulcerative conditions followed by rupture of air-containing or air-conducting organs. It causes the cellular tissue to become frothy in appearance. It terminates by simple absorption of the air, except in cases in which bacteria simultaneously enter and cause suppuration.

Tumors of the mediastinum are not infrequent, and may be of various kinds. Hare found that in 520 cases of mediastinal disease there occurred 134 cases of cancer, 98 cases of sarcoma, 21 cases of lymphoma, 7 cases of fibroma, and occasional lipomas and enchondromas.

Of the carcinomas it should be said that they are secondary and are usually of the medullary type. Of the sarcomas, the lymphosarcoma growing from the lymphatic tissue and glands of the part is most frequent.

Dermoid cysts also occur in the mediastinum, Hare having collected 11 cases. According to Marchand, Koster, and Pinders, they develop from the thymus.

Echinococcus-cysts are also of rare occurrence in the mediastinum.

THE DUCTLESS GLANDS.

Introduction.—The thyroid, the hypophysis, the thymus, and the adrenals are so-called ductless glands. Experimental physiology and clinical and therapeutic observations have demonstrated that some of these glandular organs produce, from material brought by the blood, secretions that are necessary for health and life. These secretions are passed into the blood-vessels and lymph-vessels, and are therefore called internal secretions, in contradistinction to the secretions of the usual kind which are poured out on epithelial surfaces communicating directly or indirectly with the outside of the body, and which are therefore called external secretions.¹

Morbid changes of the ductless glands may cause serious diseases by interfering with their functions and curtailing the internal secretion; or the changes may be of such nature as to lead to increased or abnormal activity and the production of an excessive or abnormal secretion, which is probably the case in the disease known as exophthalmic goiter. Theoretically one may also assume an increase or a decrease of the special substances which the internal secretion acts upon, or in conjunction with, in special or general nutrition; in this way also could be established a relative insufficiency or relative excess of the internal secretion, with consecutive symptoms of disease without the existence of morbid changes in the glands. Finally the consequences of diminished, suspended, excessive, or altered secretion may be overcome, because other structures may compensate or act vicariously for the gland affected. Our views concerning some of these things are yet incomplete, but some of the conditions referred to are illustrated in the following discussion, more particularly of the diseases of the thyroid and the adrenals.

THE THYROID GLAND.

NORMAL ANATOMY AND PHYSIOLOGY.

Development.—The thyroid gland develops from three distinct anlagen, one median and two lateral (Fig. 285), which subsequently unite (Minot¹).

The median anlage arises as a diverticulum from the floor of the pharynx, between the bases of the first and second branchial arches. In the human embryo His has shown that this diverticulum remains for some time as a hollow, bifid vesicle, connected with the pharynx by the thyrolingual duct, which opens at the foramen cecum; as a general rule, this duct persists up to the eighth week, when the median evagination has become completely separated from the pharyngeal hypoblast and embedded in the mesoblast. This is the case in most animals; but in the ammocetes and the amphioxus the thyroid empties directly into the pharynx.

¹ W. H. Howell, "Physiology of Internal Secretions," *Trans. Congress of Amer. Phys. and Surg.*, iv., 70, 1897.

² *Human Embryology*, 1892.

The lateral anlagen originate as symmetric bilateral evaginations of the posterior walls of the fourth branchial clefts. The coalescence of the three anlagen occurs in man at about the seventh week, and obliterates, as a rule, all the traces of the triple origin of the gland. The alveolar terminal pouches and epithelial bands or cords of the anlagen subsequently become differentiated into closed glandular tubules and follicles.

Gross and Minute Anatomy.—The fully developed thyroid gland consists of two lateral lobes, located on each side of the larynx and connected by a glandular bridge, the thyroid isthmus, derived essentially from the median anlage. The occasional pyramidal lobe which projects with its apex upward from the upper margin of the isthmus represents the point of ending of the embryonal thyrolingual duct.

In the newborn and young the weight of the thyroid is equal to about 0.16 per cent. of the body-weight; in the fullgrown, to 0.5 per cent. (Müller¹), the actual weight varying from 30 to 60 grams in the adult (the average weight of the thyroids of individuals living in Chicago, and between twenty and forty-five years old, being 25 grams).

Externally the thyroid is surrounded by a fibrous capsule which sends trabeculae inward, forming the connective-tissue septa of the gland. The structural details consist of a stroma containing numerous and large blood-vessels, lymphatics, and nerves, and in which are embedded glandular follicles.

The walls of the closed vesicles are formed by a single layer of cubic or cylindric cells, the outlines of which are rather indistinct, while the follicular lumen contains a homogeneous, viscid, albuminous material—the colloid substance produced by the cells. The cells may contain minute colloid drops scattered throughout their protoplasm, in which the colloid material is elaborated (the chief cells, Pozzi²); or the protoplasm may be occupied by a central mass of coalesced vacuolated colloid material, which presses the nucleus to one side—colloid cells. This colloid mass is usually extruded into the lumen of the follicle and the cell restored to its normal function and form; or it may happen under normal conditions that occasional cells become wholly converted into colloid material, in which case colloid droplets may arise in the very nucleus of the cells.

The blood-vessels are located in the interfollicular stroma; capillaries often come into immediate relation with the gland-cells (Piersol). The lymph-vessels are numerous, and begin as spaces between the bundles of fibrous tissue close to the follicles. The lymph-spaces and lymph-vessels of the thyroid, and also those around it, generally contain colloid material similar

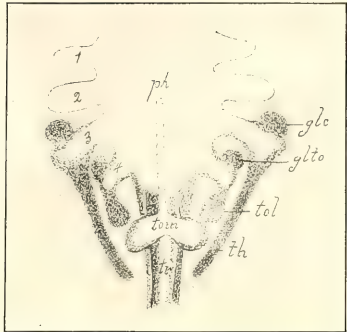


FIG. 285.—Development of the thyroid and thymus glands: *ph*, pharynx; 1-4, the four branchial pouches; *th*, thymic diverticulum; *gltc*, thyroglossal duct; *glc*, carotid gland; *tom*, thyroid median diverticulum (A. Prenant).

¹ Ziegler's *Beiträge*, xix., 127, 1896.

² *Ibid.*, xviii., 125, 1895.

to that in the interior of the follicles. The manner in which the colloid material gains entrance into the lymphatic vessels is not definitely established, but it is believed that the follicles open directly into the lymphatic vessels and thus allow their secretion to pass out (Horsley,¹ Biondi, Pozzi); the direct communication thus established may be due to the increased interfollicular pressure from the gradual accumulation of colloid material; subsequently the opened follicles most likely again close, or perhaps atrophy at times occurs (Pozzi). Others believe that only the fluid substances are absorbed by the lymphatics, there being no direct connection between these and the follicles. Horsley describes accumulations of lymphadenoid tissue around the vessels.

According to Berkeley,² the secretory nerves end in a meshwork of fibers situated almost immediately upon the basal surfaces of the epithelial cells of the follicles; the ultimate fibers of this inner perifollicular network seem to be apportioned to groups of epithelial cells and to possess a cone-shaped or rounded-end apparatus.

In addition to the normal hollow follicles containing colloid material, the stroma may present, especially in the newborn, heaps and columns of epithelial cells, which are regarded by Wölfler³ and others as embryonal remnants which have not developed into normal alveoli, and from which tumors—adenoma—may spring. In the newborn the solid cell-masses are found especially in the superficial parts of the thyroid, while in the central parts hollow vesicles have formed. This led Wölfler to distinguish between the cortex and the medulla of the thyroid. Embryonal cells are also found in the capsule of the gland.

Different from the embryonal rests are the so-called parathyroid glands of Sandström⁴ (1880) or epithelial bodies of Kohn,⁵ which consist of compact cell-masses, of a network of smaller or broader rows of cells, or of fairly regular lobules, but without vesicles and without the formation of colloid material; the amount of interstitial tissue is slight, but the blood-vessels are numerous. The parathyroid glands are recognized easiest in rabbits, in which they lie on each side of the trachea, below and away from the thyroid. In dogs the parathyroid glands lie in the thyroid; these structures also occur in the sheep, the monkey, and the human subject (Edmunds⁶); in the latter, especially in the capsule of the gland. The parathyroid glands have nothing to do with accessory thyroids (see below), but correspond more in structure and derivation (the pharyngeal epithelium) to the hypophysis (Hofmeister). Prenant⁷ has shown that in the embryo sheep the parathyroids develop as an outgrowth in the wall of the entodermal anlage of the lateral thyroid lobes. According to A. Kohn, there is one parathyroid constantly found in mammals on the lateral surface of each lateral lobe, "the outer epithelial body," and another on the mesial surface of each lateral lobe, "the inner epithelial body."

Physiology.—Experimental and therapeutic thyroidectomy and observations made in certain diseases of the thyroid have demonstrated that the function of the thyroid gland is absolutely necessary for the animal organism. Schiff,⁸ the physiologist, showed in 1856 that animals do not survive

¹ *Lancet*, 1889; *Brit. Med. Jour.*, 1890, 1892, 1896.

² *Johns Hopkins Hosp. Rep.*, iv., 281, 1895.

³ *Arch. f. klin. Chir.*, xxix., 1883.

⁴ *Upsala Läkarettörenings Föreläsningar*, 1880.

⁵ *Arch. f. mikrosk. Anat.*, xlii., 366, 1895.

⁶ *Jour. of Physiol.*, 1895.

⁷ *La Cellule*, 1894.

⁸ *Untersuchungen über die Zuckerbildung in der Leber*, 1859.

thyroidectomy, but this discovery passed unnoticed for twenty-five years. In 1882 and 1883 J. L. and A. Reverdin,¹ and Kocher² showed that a serious disease called cachexia strumipriva (Kocher), or operative myxedema, results from total extirpation of the thyroid, an operation up to that time popular for goiter. Complete removal of the thyroid, including the accessory thyroids and the parathyroids, in a large number of different animals is sooner or later fatal (Schiff, Horsley, Gley,³ Hofmeister, and many others). In the so-called acute cachexia thyropriva there are muscular tremor, clonic and often tetanic contractions of the voluntary muscles, and then paralysis, difficult respiration, salivation, diminution in the amount of urine (which becomes foul smelling), anorexia, and diarrhea, death resulting from a toxic paralysis of the respiratory centers. Similar acute severe nervous symptoms also occasionally occur in man after total removal. The acute operative tetany described assumes the more intense form in carnivora. In the monkey and in man, as well as at times in rabbits, a more chronic disease, known as myxedema, usually develops after removal of the thyroid or the suspension of its function, characterized by anemia, diminution of muscular strength, mental failure, dry skin, loss of hair, and a peculiar swelling of the subcutaneous tissue.

Many of the contradictory results at first obtained from removal of the thyroid have subsequently been explained as due to the presence of gland-remnants, to accessory thyroids, or probably to parathyroids, the effects being more or less completely compensated or materially modified by the remaining tissue. Gley claims to have shown that in rabbits complete removal of the thyroid is not fatal so long as the parathyroids remain, while removal of the thyroid and parathyroids causes typical symptoms ending in the death of the animal. Vassale and Generali⁴ also state that in dogs and cats removal of the four parathyroids produces symptoms typical of complete thyroidectomy, and that complete removal of the thyroid proper is not immediately injurious if the parathyroids, or only one of them, are left. Hence it has been concluded that in dogs and cats the symptoms attributed to thyroidectomy are in reality due to the simultaneous removal of the parathyroids. Maresch and Peucker,⁵ however, describe cases of congenital absence of the thyroid in cretins, the parathyroids being present and normal; in these cases the parathyroids did not prevent the development of cretinism (page 000), and the relation between the thyroid and the parathyroids is still an unsettled question.

It has also been shown that the hypophysis may enlarge after removal of the thyroid; in the rabbit the hypophysis is relatively five times as large as in the dog (Rogowitch), and, as stated, the rabbit suffers removal of the thyroid much better than the dog.

When the thyroid is removed from young animals, and acutely fatal symptoms are avoided, then there may follow (in young rabbits, Hofmeister) delay or arrest in development, mental dulness, alopecia, and arrested growth of the bones, due to degenerative changes in the epiphyseal cartilages; the hypophysis enlarges. In lambs von Eiselsberg found that thyroidectomy leads to the development of idiocy and to hypoplasia of the skeleton with rudimentary horns, the control-animals weighing twice as much as the

¹ *Revue méd. de la Suisse Romande*, 1883.

² *Arch. f. klin. Chir.*, xxix., 1883.

³ *Arch. de Physiol.*, iv., 664, 1892.

⁴ *Arch. Ital. de Biol.*, xxv., xxvi., 1896.

⁵ *Zeit. f. Heilkunde*, xxx., 1899.

thyroidless. The bony changes resemble histologically those of fetal rickets or chondrodystrophia foetalis hypoplastica. The whole condition is not unlike that of cretinism in man.

From these brief considerations it is seen that suspension of the thyroid function is followed by serious disturbances of nutrition that are sooner or later fatal. Schiff¹ made the brilliant demonstration that the effect of thyroidectomy in animals is completely neutralized by the injection of the extract of the thyroid or by the implantation or grafting of the gland; and these facts were applied to human pathology by Murray,² who showed that absorption of the thyroid preparations from the alimentary tract removes the symptoms of athyrosis in man. Now, it follows as a logical conclusion from its successful therapeutic action and from the evil effects of its destruction or removal that the thyroid tissue produces something essential to perfect growth and health. This important substance has been revealed by the beautiful chemical research of Baumann,³ who isolated an iodine-containing compound—thyro-iodine or iodothyron—which Hutchinson⁴ showed is found in the colloid material in the gland-follicles, and which Roos⁵ and others have shown preserves the effects of thyroid tissue.⁶ It may be concluded, therefore, that iodothyron is the active factor in the internal secretion of the thyroid gland. Recent chemical studies show that the amount of iodine in the thyroids of the inhabitants of any given district varies inversely with the prevalence of goiter in that district. H. G. Wells⁷ has demonstrated that the thyroids of residents in Chicago contain fully four times as much iodine as the glands of the goitrous districts in Germany.

The manner of action of this secretion has not yet been made clear. It may be antitoxic, neutralizing some unknown toxic substance formed in processes of normal metabolism, the retention of which causes auto-intoxication that takes the form of the striking symptoms which develop after the suspension of the function of the thyroid gland; or the secretion may be trophic, furnishing some substances necessary to metabolism of the body, more particularly, perhaps, of the nervous system. Decisive proof for either view cannot yet be given. Levin⁸ found that intravenous injection of mucin kills thyroidectomized animals in forty-eight hours, while it has no effect on healthy animals; this would indicate that the secretion of the thyroid acts upon mucin.

PATHOLOGIC ANATOMY AND PHYSIOLOGY.

Malformations.—The thyroid gland may show irregularities of lobulation. In rare cases the isthmus may be absent or pass between the trachea and the esophagus. The pyramidal process is not of constant occurrence. Partial and unilateral defects are observed, while total absence occasionally occurs in cretinism, in which case the place of the gland is usually occupied by a mass of fat; it is also usually absent in acephalics. It may be hypoplastic, and as such associated with cretinism.

¹ *Revue méd. de la Suisse Romande*, 1884.

³ *Zeit. f. physiol. Chemie*, xxi., 1896, and xxii.

⁵ *Zeit. f. physiol. Chemie*, xxi.

⁶ R. H. Chittenden, "Internal Secretions from a Chemicophysiology Standpoint," *Trans. Congress of Am. Phys. and Surg.*, iv., 1897.

⁷ *Jour. Am. Med. Assoc.*, 1897.

² *Brit. Med. Jour.*, ii., 796, 1891.

⁴ *Jour. of Physiol.*, xx., 474, 1896.

⁸ *Med. Rec.*, 1900.

Accessory thyroid glands are of somewhat frequent occurrence, and may be scattered over a rather extensive field, bounded below by the arch of the aorta, above by the base of the tongue, laterally by the large vessels of the neck, and behind by the spinal column. Accessory glands may be found in the interior of the trachea and the larynx, the anlage of which crosses the path previously occupied by the thyrolingual duct. Osler has observed accessory thyroids in the pleura. The accessory thyroid glands may be the seat of congenital or acquired enlargements of various kinds, just like the gland proper. Thyroid tissue may penetrate the trachea or larynx in postembryonal life on account of the close adhesion of the thyroid to the perichondrium and interstitial membrane; in this way arise thyroid tumors in the interior of the larynx and trachea (Paltauf¹).

The thyrolingual duct may fail to become wholly obliterated, and may remain either as a longer or shorter patent canal, or become dilated into cystic cavities. Such swellings may open spontaneously or be opened, and there may result the so-called median cervical fistula, which opens in the median line of the neck, between the hyoid bone and the sternum, commonly a little below the cricoid cartilage; such fistulous tracts are lined with stratified (Sutton) or cylindric epithelium. Many lingual dermoid cysts are also traced to this duct, and the thyroid tumors of the tongue² originate in accessory thyroids located along the path of this duct through the tongue to the foramen cecum (Fig. 286).

Circulatory Disturbances.—Passive congestion occurs in chronic heart disease, compression of the cervical veins, etc., and it seems to favor the development of goiter. During puberty and menstruation, and at the menopause, there may develop sometimes a rapid partial or general tumefaction, due to arterial hyperemia of nervous origin. The hyperemia observed in Basedow's disease is also of neurotic origin. Hyperemia is of frequent occurrence in the various forms of goiter.

Large hemorrhages occur in consequence of traumatism or in vascular enlargements; smaller extravasations can occur in connection with active and passive congestion. Hemorrhage is frequent in goiter.

Inflammations.—Inflammations of the thyroid, on the whole infrequent, appear to occur oftener when it is the seat of goiter (struma) than when it is healthy, hence strumitis is more frequent than thyroiditis. *Acute inflammation* is rarely primary, but generally secondary to injuries, such as stab wounds, or of embolic origin in the course of infec-

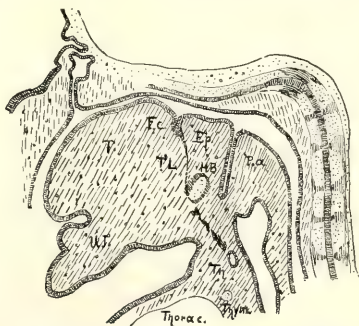


FIG. 286.—Relations of the thyrolingual duct: T, tongue; UJ, under jaw; Thorac, thoracic cavity; Ep, epiglottis; HB, hyoid bone; Fc, foramen cecum; TL, tractus lingualis; Th, thyroid gland; Thym, thymus gland; P.a, arytenoid fold (His).

¹ Ziegler's *Beiträge*, xi., 71, 1892.

² J. C. Warren, "Enlarged Accessory Thyroid Gland at the Base of the Tongue," *Am. Jour. Med. Sci.*, civ., 377, 1892.

tious diseases. Lancereaux¹ found that of 20 cases, 4 occurred in the puerperal state, 3 in typhoid fever, 2 in Bright's disease, 1 in acute articular rheumatism, 2 in pleuropneumonia, 2 in pyemia, and 6 without any direct connection with other diseases.

A large number of various kinds of bacteria have been found in thyroiditis; Tavel² found 8 micro-organisms in 11 cases; the more frequent are *Streptococcus* and *Staphylococcus pyogenes*, *Micrococcus lanceolatus*, and the bacillus of typhoid fever. The inflammations oftenest lead to abscesses, large or miliary; in inflammations of goitrous glands the pus may accumulate in cysts; extensive necrosis may take place; the abscesses may perforate into the larynx, trachea, esophagus, mediastinum, as well as externally; or be followed by absorption, calcification, and cicatrization. In 6 or 8 cases gangrene has supervened (Ewald³). Goiter may develop after thyroiditis.

Primary proliferating inflammations (not tuberculous or syphilitic) undoubtedly occur with the formation of new connective tissue, but such changes are usually considered under the comprehensive heading of goiter or struma. Vassale and Bomardini describe a case of myxedema due to chronic interstitial thyroiditis accompanied with hypertrophy of the hypophysis and of the adrenals. Riedel describes chronic inflammation of the thyroid gland leading to swelling of great hardness and firmly adherent to all the surrounding structures.

Tuberculosis of the normal and enlarged thyroid is more frequent than usually supposed; it occurs in consequence of hematogenous infection, and is generally present in acute general miliary tuberculosis (E. Fränkel⁴). It takes the form of disseminated miliary tubercles or more chronic caseous masses; it is found in 7 per cent. of the cases of pulmonary tuberculosis and phthisis (Chiari); E. Fränkel found it present 6 times in 50 cases. Usually the tubercles are situated in the periacinous connective tissue; but Cornil and Ranvier, and Baumgarten, claim that many originate from the follicular epithelium.

Syphilis of the thyroid takes the form of an irregular interstitial proliferation or of more typical gumma. Syphilis of the thyroid has so involved the function of the gland as to give rise to myxedema (Kohler), which disappeared under antisyphilitic treatment.

Kohler has described a case of **actinomycosis** of the thyroid followed by myxedema. Several instances of actinomycosis of the thyroid are described, caused by the extension of cervical actinomycosis; actinomycotic metastasis has also been described.

Echinococcus-cysts rarely occur in the thyroid; they may perforate into the trachea.

Retrogressive Changes.—The relation of the weight of the thyroid gland to that of the body in general at various periods shows that its greatest activity occurs in early life. **Atrophy** occurs in old age, and is usually characterized by an increase, relatively speaking, of the connective-tissue stroma, with sclerosis of the arteries and of the ground substance and a disappearance of the follicles by general shrinking, during which the cells become smaller and smaller, and the physical and chemical properties of the colloid altered. In old age the needs of the thyroid do not seem to be so

¹ *Traité d'anat. Path.*, 1882.

² *Die Ätiologie der Strumitis*, 1892.

³ In Nothnagel's *Specielle Pathologie u. Therapie*, xx., 1896.

⁴ *Virchow's Archiv*, civ., 58, 1886.

pronounced, and hence atrophy may occur without marked, or as yet recognized, evil effects, although some of the symptoms of senility resemble certain symptoms of myxedema. In earlier life atrophy from various, usually obscure, causes gives rise to cretinism or myxedema.

Fatty, hyaline (Fig. 287), **amyloid**, and **colloid** degenerations usually take place as secondary changes in connection with various forms of goiter.

Progressive Changes.—Regeneration¹ and compensatory hypertrophy occur to a considerable degree in the thyroid. Remnants of the gland and accessory thyroids undergo marked compensatory hyperplasia after removal or destruction of the main thyroid lobes. Halsted² has shown that in dogs experimental removal of portions of the thyroid is followed by hyperplasia of the remainder; the epithelium of the follicles becomes high and cylindric, assuming a distinctly papillary arrangement, while the colloid material is replaced by a fluid of mucoid appearance. Quite similar hyperplastic changes occur in exophthalmic goiter.

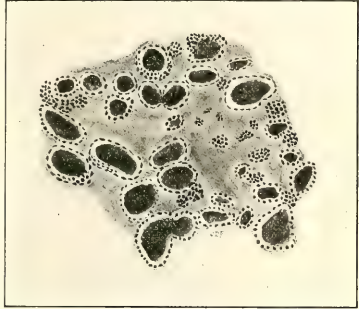


FIG. 287.—Hyaline degeneration of the stroma of colloid goiter. $\times 200$.

Goiter, struma, or bronchocele are loosely employed terms applicable to all forms of enlargement of the thyroid. Writers, especially the German, speak of malignant struma (meaning carcinoma and sarcoma), of benignant struma when referring to benign tumors, to enlargements due to hyperemia, and to the hyperplasia of goiter in the strict sense. Tuberculosis of the thyroid is spoken of as struma tuberculosa. Such a classification is unsatisfactory. True tumors and specific processes should be called by their proper names. As long as the term goiter or struma cannot be wholly dropped and an etiologic nomenclature used, it should be limited to certain hyperplasias that depend upon, as yet, obscure causes.

The hyperplasia of goiter may be nodular or uniform, partial or diffuse. The size reached may vary from moderate swellings to huge pedunculated masses. Goiter may arise in accessory thyroids wherever these may be located. It may be congenital, but it is usually acquired. The proliferation follows in the main the laws of normal growth, but the consecutive changes cause a great number of anatomic varieties.

1. Parenchymatous Goiter.—This form depends on proliferation of the parenchyma, round, oblong, and branching vesicles being formed, in which colloid material appears. The follicles are formed from solid heaps of cells through the coalescence of intracellular vacuoles containing colloid; around the central mass of colloid thus formed the cells then arrange themselves in a single layer. This may take place diffusely. The nodular parenchymatous goiter or struma nodosa consists of sharply circumscribed gland-tissue, and is attributed by Wölfler to embryonal remnants, and hence also called fetal

¹ Ribbert, *Virchow's Archiv*, cxvii., 151, 1889.

² Johns *Hopkins Hosp. Rep.*, vol. i., 373, 1896.

adenoma (adenoma foetale thyreoideæ). Atypical proliferations of embryonal gland-tissue may occur that undoubtedly would permit this interpretation; but Hitzig¹ claims that all nodules of mature gland-structure arise from preformed mature tissue.

Parenchymatous goiter is usually rather firm, fleshy, and brownish, or perhaps softer and yellowish, the follicles being, as a rule, small. If the new or old vesicles become dilated with colloid, then the most frequent form of goiter arises, namely,

2. **The Colloid or Gelatinous** (Fig. 288).—The colloid material may be secreted in part by the cells, in part result from a colloid degeneration of the cells. As the colloid material accumulates, the more fluid part is removed and the remainder changed into solid masses of varying appearance and color. The size reached by the follicles varies, but in advanced cases the cut surface is not unlike a honeycomb. In many colloid goiters the

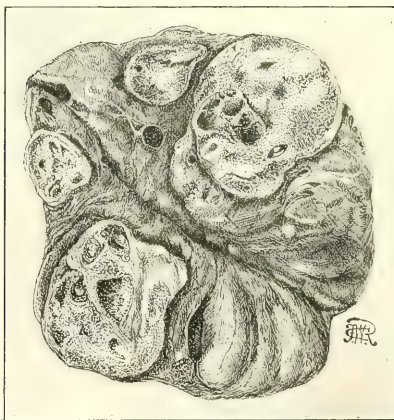


FIG. 288.—Thyroid gland with irregular nodules of colloid goiter.

stroma, blood-vessels, and lymph-vessels are diminished, and it may be impossible to find colloid in the lymph-vessels; Müller suggests that obliteration of the lymph-vessels may be the primary cause. The arteries usually show thickening of the intima and degeneration of the elastic elements (Jores). The dilatation of the follicles may proceed so far that the walls undergo atrophy, so that cysts form, lined by low or flat cells; papillary projections (compensatory?) may spring from the wall. Cysts may also arise from softening in the stroma, and coalesce with dilated follicles.

While the origin of the colloid goiter has been traced either to parenchymatous goiter or to changes in the healthy tissue, Wölfler regards it as atypical tissue proliferation composed of vesicles filled with colloid, and calls it, therefore, gelatinous adenoma (adenoma gelatinosa thyreoideæ).

3. **Vascular Goiter.**—This is in the main due to the formation of new vessels and dilatation of old. The dilatation may be transitory—a

¹ *Arch. f. klin. Chir.*, xlvii., 1894.

brief hyperemia ; or the changes may be permanent and aneurysmal, as well as varicose pouches result, associated with changes in the stroma and in the parenchyma, leading to large swellings.

Goitrous thyroids are often further changed by secondary processes. 1. Connective-tissue proliferation may form fibrous capsules around the nodules and cysts or lead to a general or irregular induration. The interstitial tissue may undergo hyaline or mucoid degeneration. 2. Cysts arise from atrophy of the interfollicular walls or from extensive colliquative necrosis. The contents vary ; the fluid may be thin, viscid, and yellowish brown, or it may be thick and jelly-like, containing cholesterolin, fat, cellular detritus, blood-pigments, etc. Impregnation with lime is not unusual. 3. Hemorrhages may occur into preformed cysts, or into the intercystic and interfollicular tissue, and give rise to hemorrhagic cysts. 4. Calcification of the interfollicular tissue as well as of the contents of the cysts occurs. An entire goiter may be calcified. Amyloid degeneration, fatty changes, and inflammation take place in goiters.

All these changes may occur in the same goiter in great variations of

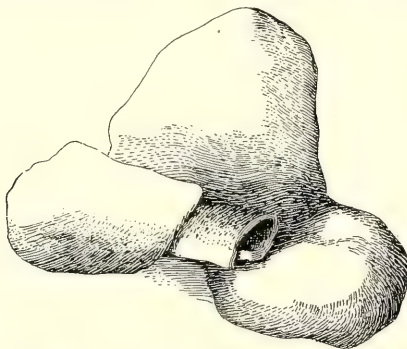


FIG. 289.—Compression of the trachea by a nodular goiter.

degree, and hence the appearances of these swellings vary much. Regenerative and hyperplastic processes are present in the healthy gland-tissue.

The consequences of goiter depend upon its form, its seat, and the direction of growth. The most frequent and the most dangerous is tracheal compression. The enlarged lateral lobes may compress it from side to side, giving it the form of a saber-sheath (Fig. 289) ; or it may become completely encircled, and unilateral growths may push it to one side. Substernal goiter may cause most marked pressure. This pressure, in addition to causing a gradual stenosis, is liable to lead to sudden asphyxia, because it causes, according to Rose, a fatty degeneration and softening of the cartilage ; the trachea becomes a flaccid tube, the lumen of which is easily obliterated by twisting or bending.

Goiters also compress the large vessels, and by gradual extension arteries and veins are pushed away from their normal location. Pressure on the vagus, the sympathetic, and especially the recurrent nerves, often causes

marked symptoms. Finally, goiters may so interfere with the internal secretion of the thyroid that myxedema or cretinism develops.

The etiology of goiter is not understood. It occurs in sporadic form everywhere. In certain districts, such as parts of Switzerland, Savoy, Tyrol, it is endemic; here it may assume an epidemic form. Careful observations have shown that the agent which causes this form of goiter is carried by the water, and that certain telluric conditions are necessary for its existence. Goiter sometimes appears in epidemic form in schools and garrisons. Recently Bruns¹ has made the suggestive observation that in young persons the medicinal use of thyroid extract causes a marked diminution and even complete retrogression of parenchymatous goiter—a retrogression to the normal of a hyperplastic organ under the influence of its own secretion—which might be taken to indicate that the goiter developed on account of increased demands for thyroid secretion.

Goiter affects the lower animals where it is common in man. It occurs oftener in women than in men, and begins, as a rule, at the time of puberty.

Tumors.—The points of distinction between simple adenoma and certain instances of the nodular form of parenchymatous goiter are not yet definitely settled. While Wölfler regards some of these proliferations and also the diffuse colloid goiter as springing from interacinous embryonal cell-masses, others regard them as pure hyperplasias of unknown causation originating from pre-existing mature follicles. Proliferating papillary-cyst-adenoma arises in the cysts that form in colloid goiter.

Adenocarcinoma of the thyroid is an interesting tumor. It arises in goitrous as well as in normal glands, and forms nodules and diffuse infiltrations, which may be soft or hard, depending on the amount of stroma, that soon infiltrate the neighboring tissue or form metastatic tumors, especially in the lungs and bones. Histologically it consists of heaps of oval or round epithelial cells in a vascular stroma; colloid changes frequently occur in the cells. At other times, perhaps in the earlier stages, the structure is more typical, presenting follicles containing colloid. Wölfler regards these tumors as springing in part from interfollicular embryonal cells, in part from fully developed follicles of benign adenoma. On account of the resemblance of the structure of the metastatic tumors, especially in bone, to normal or goitrous glands, the process has been regarded as a metastasis of goiter. Cohnheim found a bud-like projection of tumor-tissue in the inferior thyroid vein, which had undoubtedly been the source of emboli that caused the secondary growths. Eberth observed such tumors in the dog.² It is not unusual that primary carcinoma of the thyroid fails to cause enlargement of the organ; such instances have been described by Billroth and others. The gland may even diminish in size. This is important to remember in obscure cases of secondary multiple tumors. Thyroid adenocarcinoma is interesting also because von Eiselsberg³ has described a case in which operative myxedema developed after removal of the thyroid for adenoma; the myxedema improved coincidently with the development of a

¹ *Centralbl. f. innere Med.*, 1896.

² The tissue of the thyroid gland seems to possess marked proliferative capacity. Grafting of thyroid tissue results in the development of glandular masses capable of growth and function (see Christmas, *Jour. de Phys. et Path. gén.*, ii., 1900, and iii., 1901), and normal human thyroid may grow into blood-vessels, and thus give rise to osseous metastases of apparently normal thyroid tissue (Oderfeld and Steinhaus, *Centralbl. f. Path.*, xii., 209, 1901).

³ *Arch. f. klin. Chir.*, xlix., 1892.

tumor in the sternum, which on removal proved to be an adenocarcinomatous nodule with small drops of colloid; after the removal of this growth the myxedema again appeared—a unique example of a malignant tumor performing a physiologic function—*i. e.*, the internal secretion of thyro-iodin.

Cylindric-cell carcinoma with papillary outgrowths occur in the thyroid. Squamous-cell carcinoma of the thyroid may develop from inclusion of islands of epidermis in early embryonal life, but usually the cases reported of this sort are open to the criticism that they may have been secondary tumors.

Carcinoma may arise in accessory thyroids. Gulliver has described a carcinoma of the thyroid followed by myxedema, and Shattuck a case in a nineteen-year-old boy with cretinism—perhaps instances of carcinoma arising in atrophic organs.¹

Benign mesoblastic tumors are rare in the thyroid. Fibroma, chondroma, and osteoma have been described. Sarcoma in all its forms is more frequent;² it rapidly spreads out into the surrounding tissues and forms metastases; it may grow into the trachea or penetrate the jugular vein and send emboli to the lungs. In a case of Wölfler's the tumor—a giant-cell sarcoma—grew in the jugular vein and the vena cava to the heart.

CRETINISM; MYXEDEMA; EXOPHTHALMIC GOITER.

Cretinism, myxedema, and exophthalmic goiter are general diseases, the common fundamental factor in which is disturbance of the functions of the thyroid gland. Cretinism and myxedema may be regarded as due to the suspension of the thyroid function, or athyrosis; exophthalmic goiter, on the other hand, as due to perverse or excessive secretion, or dysthyrosis and hyperthyrosis.

Cretinism.—Cretinism may be defined as the arrest of mental and physical growth that develops in early life when the function of the thyroid gland is lost or greatly impaired.

The disease occurs in endemic form where goiter prevails; sporadic cretinism, like sporadic goiter, occurs here and there; the sporadic American cases have been studied by Osler.³ The anatomic changes in the thyroid that underlie cretinism are various; there may be aplasia, hypoplasia, atrophy, or goiter; the last is the most frequent in the endemic form of cretinism, and it may be of all possible forms. Cretinism is closely connected with goiter, as shown by its endemic occurrence in goitrous districts and the frequency of goiter in cretins. The experimental removal of all thyroid structures in young animals gives rise to conditions that are indistinguishable from cretinism (Hofmeister, von Eiselberg). Arrest of the growth of the skeleton has also been noticed in children after extirpation of the thyroid on account of goiter (Bruns).

Depending upon the degree of functional disturbance and upon the time at which its evil influence is felt, there are certain varieties of cretinism.

Congenital cretinism is rare, and is usually due to the agenesis of the thyroid. The skin is thick, the folds large; the limbs are short, the epiphyses swollen, but the shafts are normally ossified; the skull is broad and short, the sutures open, but the basisphenoid junction prematurely ossified.

¹ *Trans. London Path. Soc.*, xxxvii., 1886.

² See Morf, "Sarcoma of Thyroid Gland," *Jour. Am. Med. Assoc.*, 1899.

³ *Trans. Congress of Am. Phys. and Surg.*, iv., 1897.

This condition has been confounded with fetal rickets. There is arrest of cell proliferation in the cartilages, with swelling and splitting up of the ground substance, vascular enlargement of the lacunæ, and atrophy and necrosis of some of the cells (*chondrodystrophia thyropriva*).

In the majority of the cases cretinism begins at the second to the fifth year, and arrests the mental and the bodily development, producing child-like, idiotic, or imbecile persons, of short stature, brachycephaly, high cheek, and depression of the root of the nose; the skin is dry and rough, thrown into thick folds; the abdomen is large, the genitals remain infantile, and the sexual functions are usually but not always absent; the cartilages at the base of the skull are ossified too early, or there may be an early arrest in their growth; the arrangement of the cerebral convolutions is often peculiar, the mental functions fail to develop, and deaf-mutism is frequent.

Cretinism is a disease of degrees, and when the changes mentioned are less marked, the condition is referred to as *semicretinism* and the *cretinoid* state.

Myxedema; Cachexia Thyropriva or Strumipriva.—When



FIG. 290.—Hyperplasia of the thyroid in exophthalmic goiter, with lateral compression of the trachea. The thyroid weighed 100 grams. From a woman twenty years of age, who died from exhaustion due to continuous and uncontrollable vomiting in the course of exophthalmic goiter.

the function of the thyroid gland is suspended or disturbed in adults, either in consequence of disease or of operative removal, there develop severe disturbances known as *myxedema* or *cachexia thyropriva*.

Gull,¹ in 1873, first described *myxedema* as a *cretinoid* state supervening in adult women, and Ord² gave the disease its name. Reverdin and Kocher subsequently pointed out the occurrence of similar and other changes after total or partial *thyroidectomy* for goiter.

Myxedema occurs more frequently in women than in men, the proportion being about 12 to 1; it begins with swelling of the skin in the face, especially the eyelids, which spreads to other parts of the body, and which is due to deposition of a mucinous material in the collagenous tissue of the corium, the fibers of which are thick and hyperplastic, the elastic tissue being increased; the hair may fall out; there is much increase of mucus in

¹ *Trans. Clin. Soc. London*, vii., 783, 1874.

² *Ibid.*, xiii., 15, 1879.

the tissues of the body generally ;¹ there may be neuritis, fibrous arteritis, and degenerative changes in the ganglion-cells. Oligocythemia and leukocytosis are present. The expression is listless, the speech slow and blurring, the mind drowsy, and the individual may be more or less demented. In addition to the changes in the skin which are constant, there are also changes of various kinds in the thyroid upon which the disease depends. The gland is most frequently atrophic and fibroid ; goiter, pure neoplasms, syphilis, actinomycosis, may so replace the gland-parenchyma that the internal secretion of the thyro-iodin is greatly reduced or suspended. The surgical removal of the thyroid means the same as complete atrophy of the gland ; sometimes an acute tetanic condition with involvement of respiration, anemia, and exhaustion, terminating in death or in chronic myxedema, may follow thyroidectomy. The extent to which a compensation for the suspension of the function of the thyroid in man may be furnished by the parathyroids and by the hypophysis is not yet established. Treatment with thyroid gland is specific in myxedema.

Exophthalmic Goiter.—Exophthalmic goiter may be briefly defined as an intoxication of the organism by the excessive and morbid activity of the thyroid gland. The alterations in exophthalmic goiter are of a progressive and independent nature, and resemble strongly those described by Halsted and others in compensatory hyperplasia of the thyroid after removal of large portions of its structure. The gland is usually diffusely enlarged (Fig. 291) and quite firm ; nodules of various kinds sometimes occur ; late in the disease shrinking may take place. Microscopically the follicles are clothed with cylindrical epithelium which presents a papillary arrangement, and in their interior is but little or no colloid material, but more often a fluid of mucoid appearance ; the stroma is the seat of a moderate diffuse round-cell infiltration which may lead to fibroid induration, contraction, and atrophy of the epithelium² (Fig. 291). The vessels are large and numerous. Naturally these changes may occur in conjunction with others ; *e. g.*, with goiter of various kinds.

The chemical composition of the internal secretion of the thyroid in this disease has not been accurately determined, but it is generally thought that it is not only increased in quantity, but also altered in quality, because exophthalmic goiter presents other symptoms than those produced by overdoses of thyro-iodin, medicinal doses of which, as a rule, aggravate certain features of the exophthalmic disease. Operations that would tend to lessen the internal secretion of the hyperplastic gland, such as its partial removal or destruction, or diminution of the blood-supply to large portions of its tissue, usually lead to some improvement. Total thyroidectomy may be followed by complete cure. For these reasons a hyperthyroidization and a

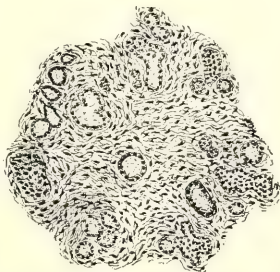


FIG. 291.—The thyroid gland of exophthalmic goiter: *a*, smaller and larger follicular spaces containing a more granular material not like colloid and clothed with a low epithelium; *b*, richly cellular, abundant stroma. $\times 125$.

¹ Halliburton, "Mucin in Myxedema," *Jour. of Path. and Bact.*, i., 90, 1892.

² Greenfield, *Brit. Med. Jour.*, ii., 1893.

dysthyroidization are now regarded as the causes of the peculiar and varied symptom-complex of exophthalmic goiter.

The changes in the other organs in this disease are not constant. Scleroderma and myxedema occasionally occur. Lesions of various kinds in the nervous system, more particularly of the restiform bodies, have been described from time to time; but sufficient data are not at hand to decide the exact relation of these changes to those in the thyroid. Hyperplasia of the thymus occurs rather too frequently for mere accidental coincidence. The causation of the anatomic changes in the thyroid is as yet absolutely hidden.

The toxic product of the abnormal thyroid acts principally upon the circulatory and the nervous systems, and also upon the skin; the most important general symptoms are fever and emaciation. Tachycardia, exophthalmos, and the goiter have long constituted the typical features of the disease. The tachycardia may become associated with actual changes in the myocardium. The exophthalmos depends upon a local vasomotor change of the blood-vessels. The symptoms on the part of the nervous system are legion: Mental excitement, sleeplessness, restlessness, and more grave disturbances; muscular spasms and paralysis; disturbances of sensation. The skin may present anomalous pigmentation, excessive sweating, circumscribed edema and erythemas, etc. The varying degrees of hyperthyroidism and dysthyroidism produce all manner of variations in the symptoms—acute attacks, chronic attacks with remissions and exacerbations, and anomalous cases occur.

THE HYPOPHYSIS.

NORMAL ANATOMY AND PHYSIOLOGY.

The hypophysis is a peculiar structure of varying size and weight (0.3–0.6 gram in man), located in the sella tureica, and composed of two lobes, the anterior or glandular and the posterior or infundibular. The glandular part is the larger. It is made up of closely packed gland-acini situated in a connective-tissue stroma containing many capillaries; in the peripheral parts of the lobe, and especially in the boundary-zone between the two lobes, the gland-follicles are often dilated and filled with colloid material, which is also found in the adjacent lymph-spaces and vessels. According to Haller, imperfect ducts open between the pia and the dura, and the secretion may be discharged here. The cells in the follicles are either polyhedral, round or oval; in the dilated follicles more cubic. In some cells—the so-called chromophile cells—the protoplasm of the cell-body, which is large, contains granules that stain reddish or yellowish with eosin; in the more common, smaller cell-forms, also known as the “chief cells,” the protoplasm is clear and not chromophile. The authors differ as to the exact significance of these cells; Flesch and Lothringer regard the chromophiles as of functional importance; Schönemann¹ contests this view, while Remy considers them as different stages of the same element. The nerves of the glandular part are derived, according to Berkeley,² from the carotid sympathetic plexus, the fibers ending in the intercellular substance.

The smaller, posterior or infundibular lobe of the hypophysis is for the most part composed of spindle-shaped large cells, which often contain pig-

¹ *Virchow's Archiv*, cxxix., 310, 1892.

² *Johns Hopkins Hosp. Rep.*, iv., 285, 1895.

ment-granules ; more irregular cells, usually regarded as nerve-cells, are also present in the region that corresponds to the infundibular duct in lower animals. The nerve-fibers end in comb-like figures and tufts not unlike the terminations in the olfactory bulbs (Berkeley).

The glandular part arises, like the thyroid, as a diverticulum from the primary oral cavity (Fig. 292). The coalescence of the folds forming the walls of the pharynx gives the glandular part of the hypophysis its intercranial position. The original channel usually becomes completely obliterated, but occasionally a trace of it is present ; according to Lanzert, the *canalis craniopharyngeus* may be recognized ten times in one hundred children. Suchannek found, in a little girl, that a column of epithelial cells surrounded by a prolongation of the dura mater extended from the hypophysis through the sphenoid bone to a cul-de-sac in the pharyngeal vault. Luschka mentions a case of *spina bifida* in which the pituitary body was pro-

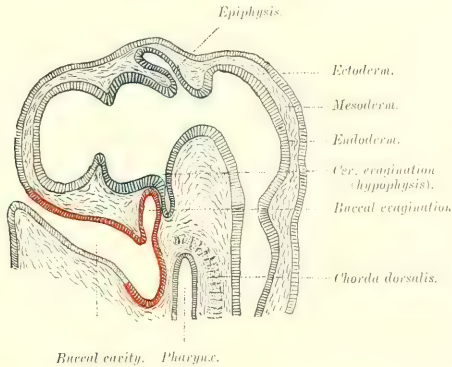


FIG. 292.—Origin of epiphysis (pineal gland) and hypophysis (pituitary gland). The blue part corresponds to the intermediate brain or thalamencephale. The red part is portion of the buccal ectoderm. The hypophysis is formed by the coalescence of two evaginations (after Mihalcovics, as modified by Charpy in Poirier's *Traité d'anatomie Humaine*).

longed into the sphenoid, and there existed an invagination of the mucous membrane upon the opposite side.

The pouch of Rathke, which marks the point of departure of the diverticulum upon the posterior pharyngeal wall, may become closed and form cysts as large as a cherry. Surrounding this pouch or cul-de-sac is the mass of lymphatic tissue known as Luschka's tonsil.

The posterior lobe descends as an outgrowth from the floor of the primary interbrain ; the stalk becomes the infundibulum, the original cavity of which is a prolongation of the ventricular cavity ; it usually but not always becomes closed. The two lobes of the hypophysis, of different structure and origin, become closely connected but do not communicate, at least not in the higher animals. In the amphioxus and ammocetes the hypophysis is represented by a duct that passes from the neural to the buccal cavity ; it is lined with ciliated epithelium, the wall contains glandular structures, and there is a group of nerve-cells around its opening into the ventricular cavity ; this duct acts as a nutrient channel, and water and pigment-granules pass

along it into the central canal; it would seem that here the pituitary body furnishes some substance necessary to the proper nutrition of the nerve substance (Andriezen¹). M. Müller concludes, from his researches upon the comparative embryology of the hypophysis, that it performs some special physiologic function, because it maintained the same characters from myxine to man.

The observations bearing upon the functions of the hypophysis were at first limited to the anterior lobe. Many facts seem to point to the close relation of this part to thyroid, which it greatly resembles in mode of origin and in structure. Thus, there occurs a compensatory hypertrophy of the hypophysis after thyroidectomy in animals (Rogowitch,² Hofmeister,³ and others); the hypophysis becomes enlarged in many diseases of the thyroid, but the exact nature of the changes, whether progressive or retrogressive, has not been determined. It has also been found (J. Schnitzler and K. Ewald⁴) that the hypophysis, like the thyroid, contains iodine, although in very minute quantity.

The fairly constant presence of changes of some kind in the hypophysis in the disease known as acromegaly, and probably also in gigantism, which is closely related to acromegaly, has been held by many to indicate that these conditions may be caused by disturbances of the metabolism of the hypophysis, which has been assumed to exercise a marked influence on the growth of the body.⁵

The disturbances of development that may follow hyperplasia of the lymphatic structures around the original pharyngeal end of the hypophysis have raised the question whether such hyperplasia gives rise to reflex disturbances of the hypophysis.

Experimental removal or destruction of the hypophysis (Horsley,⁶ Gley,⁷ and others) has not yielded any conclusive results, mainly because the severity of the operation renders it doubtful whether some of the symptoms described were due to the removal of the gland alone. The latest experiments by Friedmann and Maas⁸ on cats also yielded negative results.

The results of feeding with the pituitary body do not throw any special light on its functions (Mairet and Bosc). Szymonowicz⁹ observed a slight fall of blood-pressure and a quickening of the heart-beat after injection of the extract of the gland into the circulation of normal animals. Schäfer and Oliver,¹⁰ on the contrary, found the injections to raise the blood-pressure. Howell¹¹ made separate extracts from the glandular and the infundibular lobes, and reports that the extracts of the glandular lobe have no effect when injected alone. The extract of the infundibular lobe, however, produced a slowing of the heart-beat and a rise in the blood-pressure owing to a peripheral constriction of the blood-vessels; he concludes that the infundibular lobe has some important function different from and independent of that of the glandular lobe.

¹ *Brit. Med. Jour.*, i., 1894.

² *Fortschritte der Medizin*, 1892.

³ J. T. Putnam, *Trans. Congress of Am. Phys. and Surg.*, iv., 1897.

⁴ *Festschrift für Virchow*, 1891.

⁵ *Berlin. klin. Woch.*, 1900.

⁶ *Jour. of Physiol.*, xviii., 1895.

⁷ *Trans. Congress of Am. Phys. and Surg.*, iv., 1897.

⁸ *Ziegler's Beiträge*, iv., 453, 1889.

⁹ *Wien. klin. Woch.*, 1896.

¹⁰ *Arch. de Phys.*, 1892.

¹¹ *Arch. f. d. gesammte Phys.*, lxiv., 1896.

PATHOLOGIC ANATOMY AND PHYSIOLOGY.

Absence of the hypophysis is very rare; Boyce and Beadles¹ found it absent once in one hundred and fifty cases.

Atrophy of the hypophysis may occur; the wide variation in weight within normal limits makes it difficult to determine the presence of true atrophy. In cases of cretinism and myxedema the pituitary fossa is often of larger size than commensurate with that of the hypophysis; this has been interpreted by Hofmeister and others as pointing to a previous enlargement of the hypophysis followed by involutional changes.

Virchow has described **fatty degeneration** of the cells of the hypophysis in old people, and **amyloid degeneration** of the stroma has been observed by Hutchinson. **Calcareous masses** have been found by Vicq d'Azyr, Bichat, and Krauss.

Colloid degeneration of the glandular cells, dilatation of the follicles, and proliferation in the stroma are rather frequent retrogressive changes.

Hyperemia of the pituitary body occurs especially in the vascular

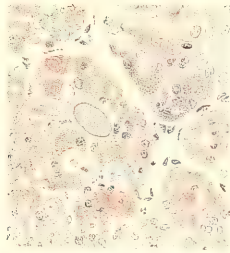


FIG. 293.—Section of enlarged hypophysis with very many chromophile cells and colloid material (in center). From a case of scleroderma with atrophy of the thyroid. Hematoxylin and eosin. $\times 175$ (Hektoen).

anterior lobe, and is characterized by increase in size and deep redness of color; it occurs in connection with general cerebral hyperemia, and with inflammatory and circulatory disturbances at the base of the brain; in some cases the resulting edema may cause softening of the gland. *Hemorrhage* into the posterior lobe was observed by Eppinger.

Acute inflammations of the hypophysis are usually due to more or less direct extension from the neighborhood; abscesses have been observed secondary to osteomyelitis of the temporal bones (Harvey). Chronic caseous *tuberculous* foci also occur,² and *gumma* has been described;³ according to Lancereaux, the hypophysis is usually indurated and enlarged in congenital syphilis.

Echinococcus-cysts of the hypophysis have been described by Sommering, and Lancereaux mentions three such cases.

Hypertrophy of the pituitary body occurs after thyroidectomy in animals, such as the dog, cat, and rabbit.⁴ In some of the experiments the enlargement was quite enormous; thus, in the rabbit Gley found the weight to

¹ *Jour. of Path. and Bact.*, i., 223, 1892.

² Boyce and Beadles, *loc. cit.*

³ Hektoen, *Trans. Chicago Path. Soc.*, ii., 129, 1897.

⁴ Rogowitch, Hofmeister, Gley.

increase from a normal average figure of 0.02 gram to 0.05 and 0.101 gram after thyroidectomy. The enlargement seems to be due to an increase in the number and size of the small nonchromophile or chief cells, and also to an increase in the amount of colloid material.

Enlargement of the hypophysis has also been observed in connection with cretinism¹ accompanied by absence or disease of the thyroid; in fibrous goiter (Pisenti and Viola); in myxedema (Boyce and Beadles); and in cachexia thyropriva.² This enlargement is not constant. In these instances there is, according to some, marked increase in the number of chromophile cells, which were regarded by Schönemann as degenerative forms. Retrogressive changes have also been observed in the stroma, and it is therefore not possible to state whether these enlargements are to be looked upon as compensatory hypertrophies or as hyperplasias of the same unknown nature as the thyroid goiter.

Pituitary struma or goiter—*i. e.*, a moderate diffuse enlargement in which colloid, fibrous, or vascular changes may predominate—is also observed independent of or in conjunction with similar changes in the thyroid gland (Virchow and others). Such hyperplasias are closely related to the more progressive and typical growths that are known as adenoma, which may reach a very considerable size; the so-called goiters are observed oftener in the insane than in the healthy (Boyce and Beadles).

Tumors of the hypophysis may spring from any part, and may represent all the more important varieties. Among those that spring from the anterior lobe may be mentioned adenoma, which is hard to differentiate from goiter, adenocystoma, and carcinoma (Boyce and Beadles). Of mesoblastic tumors observed in connection with the hypophysis may be mentioned various forms of sarcoma, lipoma,³ angioma, chondroma (Lancereaux). Hale White has described a neuromyoma composed of medullated nerves and striated muscle. Dermoid cysts have been described in connection with the hypophysis by Beck⁴ and Weigert.⁵ Langer describes two cystic tumors of infundibular origin, which he believes sprang from the infundibular canal; similar cases are mentioned by Rayer and Rokitsky.

The hypophysis may be the seat of secondary tumors, and in one instance (Wolff) of colloid carcinoma in the thyroid, the hypophysis, and in various bones, the primary focus, could not be determined. Secondary melanosarcoma may occur in the hypophysis.

The size reached by these various tumors has varied greatly. Some were very large, and caused pressure-atrophy of the bony structures of the pituitary fossa and serious symptoms from compression of adjacent structures. Any of these enlargements and tumors may be associated with acromegaly or gigantism.

ACROMEGALY.

Acromegaly (Marie, 1886) is a disease of obscure etiology, characterized by a noncongenital overgrowth of the inferior, superior, and cephalic extremities. The disease develops gradually, and is observed more frequently in youth and middle age than in advanced life.

The hands and feet become uniformly enlarged, thick, and broad, while

¹ Bourneville et Bricon, *Arch. de Neurologie*, 1890.

² Schönemann, *Virchow's Archiv*, cxxix., 310, 1892.

³ Weichselbaum, *Virchow's Archiv*, lxxv., 444, 1879.

⁴ *Zeit. f. Heilkunde*, iv., 1883.

⁵ *Virchow's Archiv*, lxx., 219, 1875.

the normal proportions between the individual parts are maintained. The head increases in size, the lower jaw becomes elongated and protruding (prognathism), the teeth separated, and the lower half of the face broad. At the same time there is a marked enlargement of the nose, lips, ears, neck, tongue, and pharynx; frequently there develops spinal deformity, more especially a cervicodorsal kyphosis. Amaurosis and other cerebral symptoms are also observed.

According to the anatomic investigations by Arnold,¹ Marie and Marinesco,² and others, the increase in the size of the extremities is due especially to bone-changes. The bones become thick, and covered with nodular and pointed outgrowths (Fig. 294). Any actual increase in the



FIG. 294.—Cranium of acromegaly (specimen belongs to Dr. L. J. Mitchell, Chicago).

length of the bones has not been demonstrated, and von Recklinghausen³ has therefore proposed to name the disease pachyakria. Arnold found degenerations of the vessels, muscles, and nerves of the affected extremities, while the bones were the seat of a hyperplastic osteitis that may assume either a hard or a soft form.

Changes in the hypophysis are found in a large percentage of the cases, such as hypertrophy; various processes resembling those observed in goiter, colloid degeneration, atrophy, sclerosis, vascular hyperplasia; in other cases the condition has been diagnosed as adenoma, as sarcoma, and as glioma. In many of the cases the hypophyseal enlargement gives rise to distinct compression symptoms. The sella turcica is, as a rule, excessively large (Fig. 295).

The etiology of acromegaly is enigmatic. The tendency is to regard the disease as a "trophoneurosis" dependent upon various diseases of the hypophysis, which lead to the interference or suspension of its functions.

¹ Ziegler's *Beiträge*, x., 1, 1891.

² *Arch. de méd. exper.*, iii., 1891.

³ *Virchow's Archiv*, cxix., 36, 1890.

Others claim that the lesions of the hypophysis are secondary to the general disease, because acromegaly occurs without recognizable changes in the hypophysis (Virchow, Pel, etc.); and the hypophysis may be completely destroyed (Weir Mitchell), or the seat of tumors and other changes (Packard and others), without the development of acromegaly; experimental removal of the hypophysis has been negative so far as the development of acromegaly and other gross changes are concerned.

Le Count¹ concludes a study of the anatomic changes in acromegaly as follows:

1. The cases of acromegaly associated with true tumor of the hypophysis are certainly not as numerous as has been heretofore supposed.
2. There is not as much constancy in the pathologic condition of the



FIG. 295.—Base of skull of acromegaly; the sella turcica is much widened (specimen belongs to Dr. L. J. Mitchell, Chicago).

hypophysis as there is in enlargement of the heart, the thyroid gland, and the sella turcica.

3. Acromegaly does not depend, at least not solely, upon abolition of any function of the hypophysis.

4. It is not at all improbable that proliferation of the histologic elements of the hypophysis may be instituted in some cases by a primary enlargement of the sella turcica; in other cases an edema or hemorrhage ex vacuo.

5. We have no reason for supposing that enlargement of the sella turcica may not be as constant an occurrence in acromegaly as the changes in other bones, or that it might not take place from a similar cause or causes.

Oestreich and Slawyk² record a case of giant growth in a boy, four years old, with a cystic psammoma, as large as a small apple, of the pineal gland, the hypophysis being normal. Concerning similar and other lesions of the pineal body, see reports by Ogle and others.³ Some form of

¹ *New York Med. Jour.*, 1899. See also Hinsdale, *Medicine*, v., 1898; and Brooks, *Archives of Neurology and Psychopathology*, i., 1898.

² *Virchow's Archiv*, clvii., 475, 1899.

³ *Trans. London Path. Soc.*, 1., 1899.

giant growth has been observed recently in connection with three cases of tumor of this body (Ogle, Oestreich and Slawyk, Heubner).

THE THYMUS.

NORMAL ANATOMY AND PHYSIOLOGY.

The thymus develops from the entoderm or hypoblast of the third gill-clefts (Fig. 285). In mammals each of the third clefts forms a tubular prolongation, with a narrow lumen and a thick epithelial lining, which grows down along the side and in front of the trachea, and coalesces with its fellow. Vascular connective tissue grows into the epithelial anlage, and small round lymphoid cells accumulate in the form of the follicles characteristic of lymph-glands (Kölliker); the original epithelial cells become smaller and smaller, their outlines disappear, and finally the remnants coalesce to form concentric laminated bodies of keratinized epithelial cells, not unlike corpora amylacea or the epithelial pearls of carcinoma, and known as Hassal's bodies. The concentric bodies are regarded by Afannasiew as due to proliferation of the vascular endothelium. Calcification often occurs in Hassal's bodies.

By its arrangement the fibrous connective tissue divides the organ into macroscopic lobes and microscopic lobules. The lobules present a distinct lymphadenoid structure, with a richly cellular cortex and a less dense medulla. Here and there in the follicles are found Hassal's bodies.

The thymus is rather a soft pinkish structure, from which more or less milky juice can be expressed. It lies in the anterior mediastinum, behind the upper part of the sternum and over the large vessels, reaching from the lower margin of the thyroid down upon the pericardium. It consists usually of two large flat lobes, which touch along their median borders. Small accessory thymic glands may occasionally be found about the periphery of the thymus body. It weighs about 24 grams at birth; at the end of the second year it weighs about 26 grams (Vierordt). It then remains as such up to the time of puberty, when it begins to undergo a second metamorphosis, and at the end of the twentieth year it has become almost completely replaced from below upward with fat-tissue. The retrosternal thymic fat-body retains the form of the thymus, and in it remnants of the lymph-follicles as well as of Hassal's bodies are always present.¹ Physiologic involution or atrophy of the thymus is not constant; the organ may persist as a collection of lymph-follicles into advanced life, or the remnants in the once atrophic organ may undergo hyperplasia.

The thymus may be completely absent (Bischoff, Friedländer); it may be larger or smaller than the normal average, and it may present unimportant variations in form and outline.

The exact role played by the thymus in the organism during the period of its existence as a lymphatic tissue is not known. The early extirpations of the thymus by Friedleben² were not followed by any symptoms that could be traced to its absence. Tarelli³ extirpated the thymus from dogs without fatal result, and he did not reach any conclusion as to the physio-

¹ Waldeyer, *Centralbl. f. med. Wissenschaften*, 1890.

² *Die Physiologie der Thymusdrüse*, 1858.

³ *Trans. Ninth International Medical Congress*, ii., Rome, 1894.

logic action of the organ. Avelous and Billard¹ found from the experimental removal of the thymus in frogs that it is necessary for the life of this animal, its removal leading to auto-intoxication. Svehla² found that large doses of watery extract of human and animal thymus glands injected into the veins of dogs cause death from dyspnea. This observation, if confirmed, may throw light upon the cause of "thymic death" (see below). Baumann found small amounts of an iodine-containing substance in the thymus. Beard³ has advanced the theory that the thymus is the parent source of all leukocytes.

PATHOLOGIC ANATOMY AND PHYSIOLOGY.

In asphyxia of the newborn the **venous hyperemia** may render the thymus rather soft and deep red in color. Venous congestion from this and other causes may give rise also to punctiform and larger hemorrhagic extravasations, subscapular or parenchymatous. **Hemorrhages** of varying extent also occur in the hemorrhagic diathesis (Pean), due to congenital syphilis or other causes.

Jacobi⁴ has described lesions of the thymus in diphtheria that undoubtedly are **focal necrosis**, with nuclear fragmentation, similar to those that occur regularly in the lymph-nodes and in many parenchymatous organs in this disease.

Inflammations of the thymus are not frequent. Great care must be taken not to mistake the grayish or yellowish juice characteristic of the normal thymus for inflammatory exudate or purulent accumulations. The inflammatory process may be due to extension from the neck, or from the pleura, mediastinum, or pericardium (Jacobi); or the infection may be of hematogenous origin, as in the case of metastatic abscess in pyemia. Abscesses of the thymus have been observed by Purkhauer to perforate into the bronchi, and by Hasse into the trachea.

Tuberculosis of the thymus occurs, in isolated instances, either in the form of miliary tubercles or larger caseous foci (Demme, Jacobi, Friesethau).

Syphilis of the thymus may appear in infants with congenital syphilis, in the form of more or less characteristic gummas, which may soften and give rise to cavities not unlike abscesses (Dubois's abscesses); or in the form of a more diffuse connective-tissue proliferation with induration (Jacobi, Mewis, etc.). The thymus may be large and soft, richly cellular, with much milky fluid in congenital syphilis, but without at the same time containing lesions. Streptococci were cultivated from thymic abscesses by H. G. Wells⁵ in a case of mixed intra-uterine infection with streptococci and staphylococci in congenital syphilis.

Tumors.—The thymus furnishes quite a number of the mediastinal tumors; dermoid cysts, with yellowish-white fatty and granular detritus as contents, at times mixed with hair, originate in embryonal tissue persistent from the time the thymus was an epithelial organ (Marchand); carcinoma occasionally develops from similar epithelial remnants. The thymus is also the seat of lymphosarcoma, which here assumes a flat, smooth form, often adherent to the pericardium, with a homogeneous cut surface, in contradis-

¹ *Arch. de Phys. norm. et path.*, 1896.

² *Wien. med. Blätter*, 1896.

³ *Lancet*, i., 1899.

⁴ *Trans. Assoc. of Am. Phys.*, iii., 297, 1888.

⁵ *Jour. Am. Med. Assoc.*, 1897.

tion to the nodular lymphosarcoma that originates in the lymphatic nodes. The differential diagnosis between such tumors of the lymphatic nodes in the mediastinum and of the thymus may not be possible; the presence of Hassal's bodies may point to the thymus as the place of origin. Oestreich describes a sarcoma originating from a persistent thymus in a man of seventy. Other forms of sarcoma also occur.

The thymus may become greatly enlarged from leukocytic infiltration in leukemia, and it may participate in the more or less general lymphatic hyperplasia of pseudoleukemia.

Angioma has been observed in the thymus by Osler.¹

Chiari describes peculiar cysts in the thymus, composed of cavities clothed with many layers of flat epithelium and containing genuine thymus-tissue, which seemed to have grown through the wall from the outside. He regards the growth of thymus-tissue into Hassal's bodies as the beginning of such cysts. Probably the so-called Dubois's abscesses are cysts of this kind.

Lochte² describes an enlarged thymus, in a man twenty-one years old, composed of closely packed epithelioid cells in a connective-tissue stroma. Schuhartz has found similar changes in leukemia (epithelioid transformation of thymus).

Enlargements of the thymus may, when marked, cause pressure upon important structures in the vicinity—the nerves and large blood-vessels, the trachea, the bronchi, and esophagus—and some of them may grow by extension to involve directly the same organs. Clinically they are consequently usually classified as mediastinal tumors.

Hyperplasia.—As already indicated, the size of the thymus may vary much. It may be congenitally large, or hyperplasia with retention of the normal structure may occur after birth and after the period for the normal involution of the gland. Thymic hypertrophy, from as yet unknown causes, often associated with a general lymphatic hyperplasia, has attracted notice especially on account of its relation to paroxysmal dyspnea ("thymic asthma"), and to sudden death from suffocation in otherwise healthy infants as well as in older persons. Kopp, as long ago as 1829, dwelt on the condition of the thymus in certain forms of convulsive dyspnea, which he called thymic asthma. Some believe that the thymus when enlarged from hyperplasia and sudden congestion may cause death from irritation of the inferior laryngeal nerves or from pressure on the pneumogastrics³ or on the trachea.⁴ Jacobi found the distance between the manubrium of the sternum and the spinal column to be 2 cm. in an eight months' child—a space readily filled by a swollen thymus. That the thymus when enlarged may in some way cause dyspnea seems evident from the cases described by Siegel⁵ and by Koenig,⁶ of children who suffered from marked dyspnea, which was relieved by removing part of the thymic glands.

Sudden death in young adults, mostly due to asphyxia, has also been ascribed to persistent and hyperplastic thymus;⁷ apparently healthy persons have died while bathing (drowning being excluded), during or after surgi-

¹ *Trans. Path. Soc. of Phila.*, xiv., 270, 1891.

² *Centrabl. f. Allg. Path. u. path. Anat.*, x., 1, 1899.

³ Holt, *Diseases of Infancy and Childhood*, 1897.

⁴ Grawitz, *Deutsch. med. Woch.*, 1888; Riedert, *Centrabl. f. Kinderheilkunde*, 1897.

⁵ *Berlin. klin. Woch.*, 1896.

⁶ *Deutsch. med. Zeitung*, 1897.

⁷ Nordmann, *Correspondenzbl. der Schweizer Ärzte*, 1889; Paltauf, *Wien. klin. Woch.*, 11, 1889, and iii., 1890.

cal operations, and under other circumstances, the postmortem findings pointing to asphyxia, the only apparent cause being persistent and enlarged thymus associated with a general lymphatic hyperplasia ("constitutio lymphatica"). Should Svehla's observations on the action of thymic extracts receive confirmation, it may be that enigmatic deaths of this kind may be due to some form of intoxication ("hyperthymization").

Persistent hyperplastic thymus glands are found rather frequently in exophthalmic goiter¹—almost too frequently, it would seem, to be regarded merely as an accidental coincidence. Some of the cases of exophthalmic goiter in which enlarged thymus was encountered died suddenly. Ohlmacher² found enlarged persistent thymus in several cases of epilepsy, associated in some with hyperplasia of the lymph-follicles in various parts of the body. Persistence of the thymus has also been observed in acromegaly, in myxedema, and in Addison's disease. No definite statement is as yet warranted concerning the relation between these diseases and the thymus.

THE ADRENALS.

NORMAL ANATOMY AND PHYSIOLOGY.

Development.—According to Balfour and Mitsukuri, and Minot,³ the adrenals develop from a mesenchymal anlage, the mesothelium on each side of the vena cava forming twisted cords, separated by blood-vessels, and from a sympathetic anlage of cells from the sympathetic ganglia. These anlages unite closely. Weldon derives the cortex from the Wolffian bodies, which secondarily encloses blood-vessels and nerves to form the medulla. Creighton and Arnold⁴ consider the distinction between the cortex and medulla as arbitrary, and the differences observed as produced by mere modifications in the arrangement of the compact parts, there being no real difference between the cells. At about the sixth month there is no special distinction between the cortex and the medulla of the embryo human adrenal.

Gross and Minute Anatomy.—The unimportant differences in the form of the two adrenals are largely due to the pressure exerted by the surrounding organs. The adrenal has a fibrous capsule, running in from which are septa containing small arteries and lymph-vessels. The adrenal vein issues from the hilum.

In fetal life the adrenal is relatively larger than in the adult. At birth the kidneys are about three times heavier than the adrenals; but in the adult the relation is as 44:1. The conjoined weight of the adult adrenals is about 9 grams, the left being, as a rule, a little the heavier. The statement sometimes made that the adrenals are larger in the negro than in the white is apparently without foundation.

The yellow cortex is composed of large epithelioid cells, which become smaller toward the medulla. Under the capsule the cells are arranged in oval masses (zona glomerulosa); then comes a layer in which the cells are disposed in a broader, cylindric manner (zona fasciculata); followed by anastomosing rows of cells (zona reticularis), which cannot be sharply sepa-

¹ Hektoen, *International Med. Mag.*, 1896.

² *Bulletin Ohio Hospital for Epileptics*, 1898 and 1899.

³ *Human Embryology*, 1892.

⁴ "The Goulstonian Lectures on the Suprarenal Bodies," H. D. Rolleston, *Brit. Med. Jour.*, 1, 1895.

rated from the medulla. Between the radiating cell-masses run connective-tissue partitions containing blood-vessels and lymph-vessels. The cells in the outer part of the cortex normally contain fat, while the inner cell-layers contain pigment-granules that stain brown with chromic preparations.

The cells of the medulla are of different forms, polygonal and oval; but the outlines are hard to make out; some are said to be branched. When fresh they stain brown with chromic solutions; alcohol extracts the chromophile substance, which varies in amount in different cells. Creighton¹ states that the brown color also occurs in the nuclei as well as in the contents of the vessels. According to Vulpian² and to Virchow,³ the medullary cells stain blue with persulphate, and green with perchlorid, of iron. The medulla contains blood-sinuses, which receive the arterioles of the cortex and empty into the central vein, which is surrounded by a mass of smooth muscular tissue. The sinuses have thin walls of endothelial cells. Occasional adrenal cells have been observed in the adrenal vein, and red blood-corpuscles occur within and between the adrenal cells. Manasse⁴ found buds or strings of cells passing through the walls into the lumen of vascular spaces, and also free cells floating in the blood or spread on the inner surface of the wall; the projecting cells seemed to be pouring out a brown hyaline material (seen only in chromic preparations), and cells without membrane were demonstrated to communicate directly with the homogeneous masses; he also found slits in the vascular walls, through which brown cells seemed to pour the hyaline material into the blood. Both Gottschau and Manasse found small, hyaline, colorless special masses in the adrenal vein of living rabbits and dogs. The precise significance of this close relation of the adrenal cells to the veins has not yet been made out. It lies near at hand to regard the hyaline material as the internal secretion of the medullary cells, which is passed directly into the blood, provided that the appearances described are not artefacts.

There are numerous nerve-fibers in the medulla ending in fine inter-cellular fibrils. The existence of ganglion-cells in the medulla has long been claimed, but some deny their presence. Ganglion-cells also occur in and upon the capsule.

Hill (quoted by Rolleston) concluded from the presence of mitoses in the deeper parts of the reticulate zone that the growth of the adrenal occurs in this situation, the cells passing inward and outward. Gottschau, on the other hand, believes that the young cells form in the zona glomerulosa.⁵

Physiology.—In 1856 Brown-Séquard showed that extirpation of the adrenals is fatal to the animal; he concluded that suppression of their function is more rapidly fatal than suppression of the urine, and that it was the function of the adrenal to modify or destroy certain substances in the blood. The results of Brown-Séquard's experiments were frequently questioned (Harley, Schiff, Nothnagel, Tizzoni, Semmola), but recent investigations have finally corroborated his statements (Szymonowicz⁶ and others).

¹ *Jour. of Anat. and Physiol.*, xiii., 51, 1878.

² *Compt. rend. de l'Acad. des Sci. de Paris*, xliii., 663-65, 1856.

³ *Virchow's Archiv*, xii., 481, 1857.

⁴ *Ibid.*, cxxxv., 263, 1894.

⁵ For a recent study of histology and histogenesis of adrenals, see Flint, *Contributions to Science of Medicine*, by pupils of William H. Welch, 1900.

⁶ *Arch. f. d. gesammte Phys.*, lxiv., 1896.

Many of the contradictory results reported in connection with experiments upon the adrenals are undoubtedly explainable by the frequent presence of accessory adrenals, which may undergo a compensatory hypertrophy and prevent death after supposed complete removal. The intimate relation of the right adrenal to the vena cava makes it difficult to extirpate the whole organ. Removal of one adrenal throws no light on the function of the glands; compensatory enlargement of the remaining adrenal occurs (Stilling). When attempted complete removal is followed by uncomplicated fatal result—which occurs in some animals in a day or so—then the symptoms are extreme muscular weakness, asthenia, feeble heart, and great fall in the blood-pressure. The blood of the animal is said to become toxic, but the toxemia is neutralized by the introduction of adrenal extract (Abelous and Langlois¹).

The researches of Oliver and Schäfer,² Cybulski³ and Szymonowicz, the results of which have received general confirmation, have established the following facts: Extract of the adrenal medulla injected into the veins causes marked slowing of the heart-beat and rise of blood-pressure of brief duration. The slowing of the heart-beat disappears on cutting the vagi, and it can therefore be caused only by stimulation of the cardio-inhibitory center in the medulla. After section of the vagi adrenal extracts cause a quicker and stronger beat by action upon the heart itself, because the effect is obtained after division of the cervical cord. It is believed that the great rise in blood-pressure is due to the contraction of the arterioles brought about either by stimulation of the vasomotor centers in the medulla or by direct action on the muscular coat. The effect is obtained after complete destruction of the spinal cord,⁴ and there is, even then, a diminution of the volume of the limb after adrenal injection, so that the evidence supports Oliver and Schäfer in the view that the extract acts directly on the muscular coat. In addition to these actions on the circulatory apparatus, a temporary slowing of the respiratory movements, which become shallow, is also noticed after injection of the extract, as well as general toxic effect on all varieties of muscle in the body (Oliver and Schäfer); Cybulski and Szymonowicz believe the extract acts on the nerve-centers of the muscles rather than directly on the tissue. The last-mentioned investigators, as well as Langlois, found that the blood drawn directly from the suprarenal vein of the living animal and injected into the circulation of a normal animal gives quite typical effects, though less in degree than the extract of the gland; blood from other veins has no such effect; thus it is shown conclusively, it would seem, that the substance is produced normally, and not by postmortem changes. It will be seen that these results bear out in a striking manner the inferences from Manasse's histologic researches that the adrenal medulla secretes directly into the blood.

From physiologic investigations it becomes intelligible why removal or disease of the adrenals produces muscular asthenia and low blood-pressure, and, in short, why the continued internal secretion of these organs is essential to the body. The exact manner of action and the final fate of the active and remarkable substance or substances produced are not yet understood. The chemists are isolating the active principle in pure form, and

¹ *Arch. de Physiol.*, iv., 1892.

³ *Wien. med. Woch.*, xli., 1896.

² *Jour. of Physiol.*, xviii., 1895.

⁴ Biedl, *Wien. klin. Woch.*, 1896.

studying its various properties and its relation to the chromophile substances in the medulla.¹

PATHOLOGIC ANATOMY AND PHYSIOLOGY.

Malformations.—Absence of the adrenals has been described by Martini and Spencer; in Spencer's case Addison's disease was present. Perhaps these were examples of extreme atrophy rather than aplasia. Hanseemann describes a case of Addison's disease with aplasia of the cortex. Lomer,² Weigert,³ and others observed more or less hypoplasia of the adrenals in anencephaly and other monstrosities. The relation, if any, between the maldevelopment of these glands and of the brain has not been established. In 5 cases of congenital hydrocephalus Czerny⁴ found aplasia of the adrenal medulla; he found that in rats the cerebrospinal lymph-spaces communicate with the lymph-vessels of the adrenal; the subject needs further study. Fusion, abnormal projections and configuration, disloca-

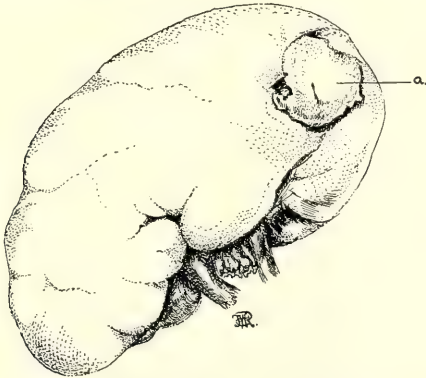


FIG. 296.—The left kidney with aberrant adrenal rest (a).

tion, and separation into several larger bodies have been described. The abnormalities of the adrenals bear no relation to those of the kidneys, but Thomas Bartholin described four adrenals in a person with horseshoe kidney.

Accessory Adrenals (Adrenal Rests).—Accessory adrenals, first described by Rokitsansky, are frequent. They are found oftenest in the connective tissue about the main adrenals, but also in the kidneys (Fig. 296), the right lobe of the liver (Schmorl⁵), along the renal vessels and spermatic veins, in

¹ For recent chemical investigations of the blood-pressure-raising constituent of the adrenal, see Abel and Crawford. *Bulletin of the Johns Hopkins Hospital*, viii., 1897; von Fürth, *Hoppe-Seyler's Zeit. f. physiol. Chem.*, xxiv., 1898; Abel, *Bulletin of the Johns Hopkins Hospital*, ix., 1898. Recently Takamine has isolated an exceedingly active crystalline substance, which he has called adrenalin (see *Therap. Gaz.*, xxv., 221, 1901).

² *Virchow's Archiv*, xcvi., 366, 1884.

³ *Ibid.*, c., 176, 1885, and ciii., 204, 1886.

⁴ *Centralbl. f. Allg. Path. u. path. Anat.*, x., 281, 1899.

⁵ *Ziegler's Beiträge*, ix., 523, 1891.

the inguinal canals (Chiari, Dagonet¹), in the broad ligaments (Marchand²). Dystopia of the cortex into the medulla may be observed near the vessels and nerves of the adrenal.

Accessory adrenals or "rests" are yellowish in color, and vary in size from the microscopic upward; their number also varies; those near the main organ are often connected with it by fibrous strings; in the kidneys they are found rather frequently, especially in the cortex, under or near the capsule, and assume the form of small round masses, which may undergo fatty degeneration and form so-called "renal lipoma"; or as larger flattened plaques of adrenal tissue placed wholly or in part underneath the capsule. Misplaced adrenal remnants may contain cells, easily recognizable as belonging to some part, more frequently the cortex, of the adrenal; or they may have, especially when a little larger, a distinct cortex and medulla.

Accessory adrenals are of importance, first, because in the young they may undergo a compensatory hypertrophy, if necessary, as, for instance, after experimental removal of the main body (Stilling); and, secondly, because they may become the origin of tumors composed of adrenal tissue. Such tumors occur in the kidney, the broad ligament, etc.

Retrogressive Changes.—Atrophy of the adrenals occurs in old age; atrophy, sometimes extreme, has been observed in cases of Addison's disease, but any definite cause could not be given.³

Cloudy swelling occurs in the adrenals under the same general conditions as elsewhere.

Fatty changes, in some degree, are nearly constant in the cortex of the adult adrenal; the fat is in the form of rather large drops, and especially well marked in the cells of the fasciculate zone. Fatty changes in the medulla are not referred to much in the literature; Atlee (quoted by Rolleston) describes their presence in marasmic infants. Fatty change has not yet been given as a cause of Addison's disease.

Amyloid disease occurs, according to Rolleston, relatively frequently; in 15 cases of general amyloidosis the adrenals were involved in 8, the degeneration being best marked on the cortex (Fig. 297). Cornil and Ranvier, on the other hand, state that the change involves especially the medullary vessels. It has been found in connection with Addison's disease.

Focal necrosis in the cortex may take place in puerperal eclampsia, chronic tuberculosis, and undoubtedly also in other intoxications and infections. In diphtheria intoxication of guinea-pigs Welch has observed a hyaline necrosis of the medullary cells. In malaria Barker⁴ found some of the cells swollen, vacuolated, and fatty, with fragmented nuclei; such changes also occurred in foci; the vessels were dilated and the endothelial cells contained pigment-masses.

Pigmentation of the medullary cells occurs under the general setting free of pigment, as takes place, for instance, in dogs after poisoning with toluyldiamin (Pilliet), and variations in the normal amount of pigment are observed.

After death **softening** rapidly occurs in the junction of the cortex with the medulla, giving rise to a cavity with uneven margins, to which viscid,

¹ *Zeit. f. Heilkunde*, vi., 1885.

² *Virchow's Archiv*, xcii., 11, 1883.

³ Carlin Phillips, *Jour. of Exper. Med.*, iv., 581, 1899.

⁴ *Johns Hopkins Hosp. Rep.*, v., 219, 1895.

brown masses adhere. This postmortem change is recognized as such by the absence of hemorrhage. It was this frequent form of apparent cyst that gave rise to the term suprarenal "capsule." Renal cysts may follow hemorrhages (Klebs, Odenius¹), abscesses, and softening in tumors (Virchow). When such cysts come under observation there may be absolutely nothing to indicate their mode of origin (Fig. 298).

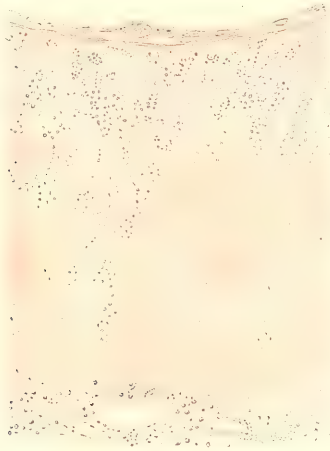


FIG. 297.—Amyloid adrenal. The degeneration affects principally the inner zones of the cortex. Hematoxylin and eosin. $\times 150$.

Disturbances of Circulation.—**Passive congestion** makes the adrenal large and brownish red. In experimental diphtheria of the guinea-pig the adrenal medulla is constantly congested and hemorrhagic. **Hemorrhage** also occurs in the guinea-pig after the injection of Friedländer's bacillus, the introduction of oil of geranium (Roger), and also in experimental pyemia (Langlois and Charrin). Hemorrhagic infiltrations may occur also in the



FIG. 298.—Cyst in the adrenal gland.

so-called hemorrhagic diathesis and after thrombosis of the veins. Severe injuries—such as fracture of the spine—are often associated with hemorrhage about as well as into the adrenal. Hemorrhages into the adrenal are not unusual during birth, especially in difficult labors and in pelvic presentations. Spencer found extravasations in the adrenal in 26 of 130 stillborn children; in 24 the extravasation was in the medulla; in half of

¹ *Nordiskt Medicinskt Archiv*, 1895.

the cases the lesion was bilateral; in 3 cases the hemorrhage ruptured the capsule. The subsequent changes may be of importance; the substitution of the clot with connective tissue might lead to induration and contraction with atrophy of the medulla, which, if bilateral, might suspend the internal secretion and lead to Addison's disease. The clots may become calcified and encapsulated (Chiari¹) or give rise to cysts.

Inflammations.—Primary acute inflammations of the adrenal are rare. Metastatic abscesses occur in pyemia. Abscesses of the adrenal may rupture into the retroperitoneal connective tissue, the colon, or the duodenum. Chronic interstitial proliferations are rare also and of obscure genesis; they lead to atrophy of the specific cells, adhesions to surrounding organs, and may be associated with Addison's disease.

Tuberculosis of the adrenal is important because of its relation to Addison's disease. Miliary tubercles develop, especially in the cortex, in general tuberculosis; but it is in the chronic fibrocaceous form that adrenal tuberculosis most frequently occurs. The bacilli are arrested in the medulla, because it is here that the process nearly always begins. The disease may be unilateral or bilateral, and not infrequently the adrenal is the only organ in which tuberculosis is found. Adrenal tuberculosis may be the starting point of tuberculosis of the peritoneum. The granulation-tissue usually forms slowly, and with time the entire adrenal becomes changed into a fibrocaceous mass surrounded by a dense scar, which may involve the semilunar ganglia and abdominal sympathetic. Softening as well as calcification may take place. Adrenal tuberculosis may be entirely latent. Rolleston found 18 cases of tuberculosis of the adrenal in 131 tuberculous cases; 11 were unilateral, 7 bilateral, but there were no symptoms of Addison's disease.

Congenital and acquired **syphilis** may cause thickening of the vessels; gumma of the adrenal has been described.

Kanthack and others have recorded the extension of **actinomycotic** processes in the liver to the right adrenal.

Tumors.—Certain tumors of the adrenal reproduce its structure in more or less typical manner. The nomenclature of these tumors presents certain difficulties, because in their morphology and in the arrangement of the cells and the stroma they resemble adenomas and carcinomas, and are frequently described as such. The more diffuse hyperplasias of this kind were long ago designated as struma suprarenalis by Virchow. In view of their peculiarities these tumors are often given more general, nonspecific names, such as adrenal tumors (*sensu strictu*), or hypernephroma as proposed by Birch-Hirschfeld.

Adrenal tumors (*sensu strictu*), **hypernephroma** of the adrenal, may occur as small, single or multiple, yellow nodules in the cortex or, less frequently, the medulla; in either case the cells may resemble in form and arrangement the cells of the adrenal cortex, and, like these, they are the seat of advanced fatty changes. Or there may be a more diffuse hyperplasia of the adrenal cortex with quite perfect preservation of its structure. Such growths may reach considerable size; they may be single or, more rarely, bilateral; at their periphery may be smaller nodules. Extensive fatty changes often take place (struma lipomatosa suprarenalis—Virchow²); in some the fibrous tissue may be in relative excess; hyaline degeneration and softening

¹ *Wien. med. Presse*, xxi., 1880.

² *Die krankt Geschwülste*, ii.

occur. Tumors are described also that resemble in structure glioma, and may contain cells not unlike ganglion-cells; these occur in the medulla, with the structure of which they have been considered as homologous, and they vary in size from that of a pea to that of a raspberry (Virchow, Marchand).

While the above-mentioned neoplasms occur mostly in a clinically latent and benign form, there are also progressive malignant tumors due to continued atypical proliferation of adrenal tissue. Those that follow more or less closely the type of the structure of the cortex present groups of flat, polygonal, fatty, and yellow cells arranged in a delicate stroma with abundant thin-walled vessels. On account of the epithelioid character of the cells these tumors are spoken of as carcinomas. Extensive fatty degeneration and softening with hemorrhagic infiltrations of the soft tumor-tissue may take place, so that the cut surface presents a variegated appearance. Malignant adrenal tumors of this character often infiltrate neighboring organs, such as the liver and the kidney. The tumor may grow into the veins and reach the vena cava; metastatic nodules may develop as well as a marked cachexia.

Malignant tumors from the medulla present at times the structure of round-cell and lymphosarcoma, which do not seem to differ materially from typical sarcomas in other tissues. Malignant adrenal tumors with giant cells have been described by Marchand and Manasse,¹ who found tumor-cells in the veins and capillaries. Tumors composed of quite typical medullary tissue have been described by Morris² and others. The tumors were composed of glandular polygonal cells with an oval nucleus and granular pigment, which turned yellow in bichromate preparations, placed between an intricate network of sinuses, capillaries, and veins containing a homogeneous material.

The adrenal rests, already mentioned, may become the point of origin of extensive tumor-growths *sui generis*. Grawitz³ was the first to demonstrate that a number of tumors of the kidney, known as lipomas, adenomas, and sarcomas, originate in misplaced adrenal remnants (*strumæ aberatæ suprarenalis renis*). Similar tumors have also been observed in the broad ligament, the liver, and other places where accessory adrenals occur, and the number of observations bearing on these interesting neoplasms has steadily increased.⁴ The tumors in question afford a striking example of the development of tumors from misplaced tissue, but the cause of the proliferation of the cells of the tumor-matrix still remains unfathomed. The cells of these tumors resemble in form and in fatty changes the cells of the adrenal cortex, and like these they are also arranged in columns and heaps in a delicate vascular stroma; the vessels often dilate to form cavernous spaces. The manner of growth is frequently atypical, and the cells may present papillary and tubular arrangements, the structure of the hypernephroma deviating more and more from the type of the mother-tissue. Lubarsch has shown that it is quite common for these cells to contain glycogen. The tumors, usually of a salmon-colored appearance, may reach great size, infiltrate the tissues and organs about them, penetrate into vessels, and form distant

¹ *Virchow's Archiv*, cxxxi., 391, 1890.

² *Brit. Med. Jour.*, i., 1893.

³ *Virchow's Archiv*, xciii., 1883.

⁴ For references, see Kelly, "Hypernephroma," *Ziegler's Beiträge*, xxiii., 280, 1898, and *Phila. Med. Jour.*, 1899.

metastases. Degeneration, softening, and hemorrhage occur; recidivation and death from tumor-cachexia are observed.

The question whether tumors composed of adrenal tissue produce the secretion of the normal adrenal, or some modification thereof, and thus cause special symptoms, has not yet been fully elucidated. The case of Felix Fränkel¹ is cited by Brüchanow² as a probable example of the stimulating influence of adrenal tumors on the circulatory system. Fränkel's case was one of bilateral adrenal sarcoma in a girl of eighteen; chronic nephritis, arteriofibrosis, and cardiac hypertrophy were present. The condition is too complicated to throw much light on this question. Neusser³ mentions clinical observations of similar import, hypernephromas being associated with cerebral hemorrhage rather frequently.

Ganglionic neuroma (Weichselbaum), ganglionic fibromyoma angioma (Payne), cavernous lymphangioma (Klebs), represent rare tumors in the adrenals.

The adrenal may become the seat of secondary carcinoma, sarcoma, and endothelioma. Secondary carcinoma may be associated with Addison's disease, as in the case of Reiche, in which the primary tumor was located in the trachea.

ADDISON'S DISEASE.

The only general disease that interference with the adrenal function can produce, as far as now taught, was described by the English clinician Addison, in 1854, and has since been known by his name. It is characterized clinically by marked emaciation, extreme asthenia, toxemic symptoms, vomiting and diarrhea, bradycardia, and, generally, by melanoderma or bronzing of the skin. It is a chronic, fatal malady.

Addison's disease in the vast majority of cases is definitely associated with gross changes in the adrenal bodies. In from 74 (Lewin⁴) to 80 per cent. (Gilman Thompson⁵) it concerns a chronic fibrocaceous tuberculosis; but simple atrophy, chronic interstitial inflammation, malignant tumors, especially secondary carcinoma, aplasia, and hemorrhagic extravasations with consecutive changes have all been recorded as more exceptional causes. Carlin Phillips⁶ reports a case of Addison's disease with simple atrophy of the adrenals; he finds 13 similar cases in the literature. The pathogenesis of the atrophy is obscure. But the existence of Addison's disease without lesion of the adrenal is generally acknowledged; in Lewin's statistics of 285 cases, 12 per cent. were of this type. It must also be added that extensive disease of the adrenals may exist without the Addisonian symptom-complex.

The theories and explanations advanced to account for the origin of Addison's disease have been numerous and varied; many bear evidences of an almost distressful ingenuity. The recent advance in our knowledge of the internal secretion of the adrenal has rendered the majority of the theories obsolete and of merely historic value.

Because Addison's disease occurs without any apparent changes in the adrenals, and because the adrenal changes present often involve the abdominal sympathetic, it was attributed to chronic degenerative and inflammatory

¹ *Virchow's Archiv*, ciii., 244, 1886.

² *Nothnagel's specielle Pathologie und Therapie*.

³ *Am. Jour. Med. Sci.*, cvi., 1893.

⁴ *Zeit. f. Heilkunde*, xx., 1899.

⁵ *Charité Annalen*, 1892.

⁶ *Loc. cit.*

changes in the semilunar ganglion and abdominal sympathetic (Wilks, Jaccoud, Tizzoni, Semmola). This "nervous theory" quite held the field until recently; but the changes described by some in the nerves are frequent in apparently healthy individuals;¹ and extensive chronic fibrous inflammation in the vicinity of the adrenals might lead to destruction of the efferent vessels, the sequence of events being comparable to Boinet's experimental ligature of the veins of the adrenals with fatal effects. Addison's disease may occur without any changes in these nerves.

More or less extensive changes in the adrenals occur without Addison's disease, and have constituted another stumbling-block in the study of its pathogenesis. Such cases may be explained away partly on the score of errors of diagnosis. There are undoubtedly anomalous instances of Addison's disease in which such conspicuous symptoms as pigmentation of the skin may be absent (Chvostek), and, obscured still further by the symptoms of the primary disease, such as carcinoma or tuberculosis, the presence of Addisonian symptoms may fail to be recognized; or the lesion in the adrenal, as secondary carcinoma, for instance, may have formed so recently before death that the symptoms had not time to develop. But in atrophy of the adrenal this explanation would not hold, and here it has been suggested that compensation may occur by compensatory hypertrophy of accessory adrenals or in some other manner not now understood.

There is therefore no absolute incompatibility between the facts of morbid anatomy and the view that Addison's disease is caused by suppression of the internal secretion of the adrenals. This view is supported by all the recent investigations into the physiologic chemistry of the adrenal. Oliver and Schäfer found that the extract of adrenals in Addison's disease did not contain the stimulating substances in that from the normal organ; and the extreme debility of patients with Addison's disease recalls the asthenia that follows experimental removal. Improvement has been reported after the use of adrenal extract. The undeniable occurrence of Addison's disease without changes in the adrenal or the surrounding structures may for the present be referred to an absolute or relative inadequacy of the adrenal secretion,² occurring under pathologic chemical conditions of the body not now understood; or it may be that a painstaking examination of the adrenal medulla may reveal chemical and histologic changes not yet observed because not looked for. It is only within recent times that the adrenal medulla has come to be regarded as the important part of the organ, and the study of the finer changes of its cells is yet new. Abel's epinephrin was obtained from the medulla; but in Phillips's case of Addison's disease with atrophy of the adrenal the histologic changes in the medulla were insignificant.

The Addisonian symptoms are primarily due to lack of adrenal secretion; the extreme debility and asthenia are attributed to the withdrawal of the necessary physiologic stimulus and vascular tonic that it supplies. It must be remembered that the adrenal secretion is probably not merely a chemical antidote, because it has such marked and definite action on healthy animals. Whether the deficiency of the internal secretion leads to toxemia is, however, as yet an undecided question. It is tempting to assume that in the absence of its tonic and regulating effects toxic substances gradually develop and cause the vomiting and the diarrhea. The blood of acapsulated animals is

¹ Hale White, *Jour. of Physiol.*, x., 1898.

² Adami, *Trans. Congress of Am. Phys. and Surg.*, iv., 1897.

more or less toxic ; but Oliver and Schäfer found that the urine in Addison's disease does not contain any special toxic bodies.

The pigment of Addison's disease is deposited in the rete. The derma contains more pigment-carrying cells than usual ;¹ and pigmentation of the mucous membrane of the mouth, eye, and vagina occurs, especially about small local lesions. It is thought that the pigmentation is derived from the hemoglobin, but the steps and the places of transformation are not known. Rolleston suggests that the constant influence of some toxic substance on the sympathetic nervous system is the underlying factor, especially inasmuch as clinical evidence points to the nervous system as having considerable influence on pigmentation of the skin.

Among the anatomic changes of other organs in Addison's disease may be mentioned enlargement of the intestinal lymph-follicles and of the spleen, which is fairly constant. Accidental lesions of various kinds have been observed. Secondary degenerations occur in the spinal cord as in pernicious anemia. Tuberculosis in other organs is naturally a very frequent finding.

¹ Von Kahlden, *Centralbl. f. Allg. Path. u. path. Anat.*, vii., 1897.

THE URINARY ORGANS.

THE KIDNEY.

Development.—The kidney is developed as an outgrowth from the lower end of the Wolffian duct of the embryo—the so-called mesonephros. The ureter is also formed from the Wolffian duct, and for a time empties conjointly with it into the bladder. The bladder represents the middle segment of the allantois, the upper segment constituting the urachus. The lower fold of the allantois becomes the first part of the male urethra and the entire female urethra. The anterior portion of the male urethra is formed by the folds of integument which produce the penis.

The kidney and ureter are mesoblastic in origin; the mucous membrane of the bladder, the female urethra, and the first portion of the male urethra are derived from the hypoblast. The anterior portion of the male urethra is epiblastic in origin.

Position.—The position of the kidneys with relation to the vertebral column is somewhat variable. Usually the right extends from the twelfth dorsal vertebra, or the disk between it and the first lumbar, to the middle or lower end of the third lumbar; the left from the intervertebral disk between the eleventh and twelfth dorsal vertebræ to the upper or middle portion of the third lumbar vertebra. Thus the right kidney is nearly always somewhat lower than the left. On account of the obliquity of the ribs the kidneys are almost completely enclosed by them, and project only slightly beyond the twelfth rib.

Size and Weight.—The kidneys measure each from 10 to 12 cm. in length, from 5 to 5.6 cm. in width, and 3.38 cm. in thickness, the left being slightly larger than the right. The weight, according to Thoma, is: for the right kidney, 152 grams in men and 144 grams in women; for the left, 164 grams in men and 148 grams in women. Baduel¹ gives the following weights and measures: for the right, 110 to 120 grams, and for the left, 120 to 130 grams in men, and 110 to 115 grams for the right and 115 to 120 grams for the left in women. In youth the right kidney is 8.5 cm. long, 4.5 cm. wide, and 2.5 cm. thick, and weighs 64 grams; the left is a little larger and heavier. In childhood the corresponding figures are: 6.5 to 7 cm., 3.5 to 4 cm., and 1.5 to 2 cm.; the weight, 35 to 40 grams. In the newborn the figures are: 4.2 to 4.5 (4.5 to 5), 2.2 to 2.5, and 1.5 cm.; the weight is from 10 to 12 grams. In the newborn and in children the relative proportion of the kidney to the body-weight is much greater than in adults.

Appearance.—The surface of the kidney in adults is smooth; in infants and young children the lobulation existing in fetal life is more or less preserved, according to the age. Occasionally it persists through life.

On section the surface of the kidney presents an outer, band-like zone, the cortex, and an inner part, the medulla. The appearances of these two are

¹ "Topografia e percussione dei reni," *Il Policlinico*, i., 297, 367, 1894.

very different, a fact dependent upon difference in the arrangement of the uriniferous tubules. Normally the relation between the cortex and the medulla is 1:3.

The histologic structure of the kidney need not be detailed here, as it may be found in any text-book on histology.

Malformations of the Kidney.—Congenital malformations and other anomalies are not uncommon in the kidneys. Total absence, or **aplasia**, of the kidneys is rare, and has been observed only in nonviable monsters. Absence of one kidney, usually the left, is not infrequent. In such cases the existing kidney is enlarged, and generally performs the renal functions adequately.

Congenital **smallness** of both kidneys has been noted, but the hypoplasia more often affects only one organ, and may be due to faulty development, to congenital smallness of the renal artery, to intra-uterine inflammatory changes, or to congenital stricture of the ureter.

A comparatively frequent malformation is partial union or fusion of the

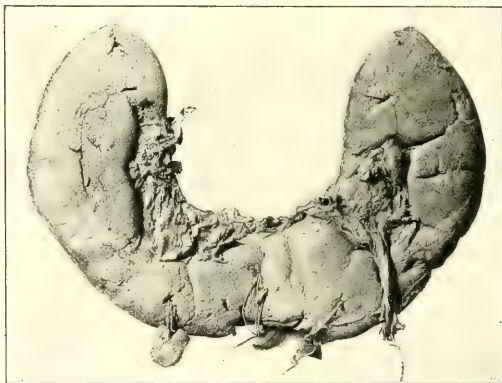


FIG. 299.—Horseshoe kidney.

kidneys, best illustrated in the **horseshoe kidney** (Fig. 299). In this the two organs are fused at either the lower or the upper poles, more commonly at the former. The union may be by means of a fibrous band or by a bridge of true renal tissue, and usually is in front of the aorta and the inferior vena cava. The horseshoe kidney is often placed lower in the abdominal cavity than normally, at times near the promontory or in the hollow of the sacrum. When in the last-mentioned position the presence of the organ may interfere with labor. Extensive concrescence is generally associated with anomalies in the number and distribution of the ureters and blood-vessels. The cause of horseshoe kidney is a disturbance occurring very early in embryonal life, whereby the outgrowths from the two Wolffian ducts come to lie too close together and are able to coalesce.

Another common anomaly, to which reference has already been made, is the **preservation of the lobulation** existing in fetal life and for a year after

birth. The lobulated kidney is marked by a number of shallow furrows, irregular in course and cutting each other in various ways.

Supernumerary kidneys have been observed. The accessory organ may be adherent either to one kidney or the other, or it may be free. In a case observed by Hanseman¹ there were three kidneys—one on the right side, normal in position, and two on the left side. The smaller of the two latter represented the normal organ. Its ureter emptied into the pelvis of the third kidney. The latter received two vessels—one from the lower part of the aorta and the other from the right iliac artery—and could be considered as equivalent to the bridge that unites the two organs in horseshoe-kidney. A case of triple kidney was also reported long ago by Thielmann.² At times the kidneys and suprarenal gland, normally separated, are fused.

Malpositions of the Kidney.—These may be congenital or acquired. *Congenital malpositions* are more frequent in men than in women (20 : 9).³ In 80 per cent. of the cases the malposition affects the left kidney, which is placed lower than normally, and may be near the promontory of the sacrum or in the pelvic cavity. The organ is, as a rule, permanently fixed in its abnormal position. The ureter and blood-vessels generally have an abnormal origin, or point of entrance, and are increased in number, while the ureter is shortened. Very rarely one kidney—also generally the left—is transposed to the opposite side, and is then placed below the other, to which it is usually, but not always, adherent by fibrous or renal tissue. The suprarenal body does not seem to share in the misplacement. In rare cases both kidneys occupy an abnormal situation.⁴

The presence in the renal substance of aberrant portions of suprarenal tissue is a malformation of great importance, as it is not rarely the starting point of renal tumors. It will be discussed at greater length under the subject of Tumors of the Kidney.

Acquired malposition is most frequent in the female sex between the ages of twenty and fifty. In the vast majority of cases it affects the right kidney, rarely both organs, and least frequently the left alone, though in some of the statistics bilateral movability is given as less common than movability of the left alone. The following figures are quoted from Wolkow and Delitzin⁵ and from Freitag.⁶ In 91 cases of floating kidney, Ebstein found the right affected in 65, the left in 14, and both in 12; but the majority of other observers give the proportions a little differently. Thus :

Fritz	19 right,	4 left,	7 bilateral.
Schultze	37 "	6 "	7 "
Landau	40 "	2 "	3 "
Roberts	42 "	9 "	14 "
Schütze	65 "	18 "	14 "
Keen	76 "	7 "	4 "

Movable kidney has been observed to occur in children. Comby⁷ reported 6 instances, all in girls, 4 being from ten to sixteen years of age. The other 2 were discovered at autopsy in syphilitic infants aged one and

¹ *Berlin. klin. Woch.*, Jan. 25, 1897.

² *Med. Chi. Review*, Jan. 27, 1837.

³ Stern, *Inaug. Diss.*, Berlin, 1869.

⁴ Kelly, *Ziegler's Beiträge*, xxiii., 280, 1898; Weinberg, *Bulletin de la Société anatomique*, lxx.—lxxii., 1895. ⁵ *Die Wanderniere*, Berlin, 1899.

⁶ *Vorträge über Nierenkrankheiten*, Leipzig, 501, 1898.

⁷ *Med. News*, July 10, 1897.

three months respectively. In them the condition was bilateral. Rosenthal¹ has also recorded the occurrence of movable and floating kidney in children. Hollederer² found only 5 in 100 children between one and eighteen years of age in whom the kidney was movable. It should not be forgotten that the kidneys are normally slightly movable.

Normally the kidney is held in place by a variety of means, which have been most carefully studied by Gerota.³ The most important factor is the fibrous tissue (fascia renalis), a part of the subperitoneal fascia situated between the peritoneum and the fatty capsule of the kidney, which splits into an anterior layer (lamina prerenalis, fascia renalis anterior) and a posterior (lamina retrorenalis, fascia renalis posterior). These two layers unite at the upper and lower poles of the kidney. The posterior layer is intimately connected by means of numerous septa with the fascia of the quadratus lumborum and the psoas magnus muscles, and with the kidney, especially at the hilus. The retrorenal fascia, by its adherence to the abdominal wall, is one of the most important, if not the most important, anchor for the kidney. As the adhesion of the fascia to the posterior wall is firmer than that to the kidney, the latter can move within its fascial covering, but cannot be displaced together with it. The peritoneum is not of much significance as a means of retaining the kidney.

According to Glénard, the kidney is also held in place by a ligament passing from the upper pole to the suprarenal gland (ligament rénosurrénal adventu). Whether the renal vessels play any role in the fixation of the kidneys is undecided. Gerota thinks that they do so only after the kidney has been displaced, while Schmidt believes that without some congenitally abnormal length of the vessels movable kidney is an impossibility. The small vessels passing from the lumbar region to the capsule of the kidney probably help to fix the organ.

An important influence in the retention of the kidneys in their normal place has been assigned to intra-abdominal pressure (Schwerdt). Glénard also attributes some influence to the aspirating action of the diaphragm; but this cannot be of much significance, as the descent of the diaphragm in respiration would act in the direction of displacing the kidney.

According to Wolkow and Delitzin,⁴ the shape of the so-called *paravertebral niche* or *hollow* is of great moment in the fixation of the kidney. This niche, which is the deepest recess of the posterior abdominal wall, varies markedly in shape in different individuals. In well-formed persons it is broad above and becomes narrow downward, is relatively deep, and pyriform or funnel-shaped. In women the niche is naturally less broad above and more widely open toward its lower extremity. In cadavers in which the kidneys were abnormally movable the niche was shallow, distinctly cylindric, and open downward. When only one kidney was movable the niches were decidedly asymmetric. The abnormal shape of the paravertebral niche is probably a congenital character; this also explains why floating kidney may be hereditary in families.

Aside from the abnormality in shape of the paravertebral niche, there are a number of factors that favor the production of floating kidney. The most important is relaxation of the abdominal walls, brought about especially by repeated pregnancies. In the writer's experience, however, floating kidney has been almost as common in single as in married women. Tight lacing is a probable factor in some cases. Regarding the mechanism of tight lacing, it is believed by Wolkow and Delitzin that the practice becomes harmful by bringing about a change in the paravertebral niche. Bache and Lormhoff,⁵ however, are right in maintaining that the influence of the corset has been exaggerated. They found a palpable right kidney in 6 out of 24 Samoan women who had never worn European dress. Landau has shown that uterine displacements, on account of the intimate relation of the uterus to the bladder and the ureters, may cause movable kidney. Traumatism and the lifting of heavy weights also play a role, but probably are of minor

¹ *Therap. Monatshefte*, xii., 343, 1896.

² *Inaug. Diss.*, Erlangen, 1897; *Centralbl. f. d. Grenzgebiete d. Med. u. Chir.*, ii., 42, 1899.

³ *Archiv. f. Anatomie u. Physiologie*, Anat. Abth., p. 265, 1895.

⁴ *Loc. cit.*

⁵ *Deut. med. Woch.*, No. 32, 1898.

consequence, else movable kidney would be common in men. The wasting of the fatty capsule around the kidney is also a predisposing cause. Sometimes the organ is dragged down by tumors. Large accumulation of fluid in a pleural cavity is also said to favor, by mechanical action, displacement of the kidney.

The fact that the right kidney is more frequently found floating than the left is explained in various ways. Normally the right kidney follows the descent of the liver during respiration. The left kidney is more firmly anchored by its shorter renal artery, although this is not a factor of much moment. Anteriorly the left kidney is in relation with the pancreas, the spleen, and the descending colon; and the peritoneal covering holds the kidney more firmly in place on the left side than it does on the right. Posteriorly the fixation of the two kidneys is the same.

The relation of the displaced kidney to the peritoneum is of importance. Either the organ is freely movable behind the peritoneum, or it carries the latter in advance of itself in such a manner that it and its vessels are completely surrounded by peritoneum—an apparent mesonephron being formed. There is no true mesonephron in the sense that the kidney is swung on a peritoneal stalk, in the tissues of which the vessels run. The mesonephron is merely a sac, comparable to that of a hernia, and not homologous with the mesentery.

The degree of movability of the kidney varies. It is customary to apply the term *movable* to the kidney when the organ can be readily felt, but cannot be pushed below the level of the umbilicus; and to speak of *floating* kidney when the organ possesses a higher degree of movability. Sometimes this movability is so great that the kidney may occupy almost any part of the abdomen. In rare cases the kidney becomes fixed in an abnormal position; adhering, for example, to the gall-bladder, the colon, or the anterior abdominal wall.

The displacement of the kidney may produce torsion or bending of the ureter, and lead to an intermittent or a permanent hydronephrosis. Albarran believes that the hydronephrosis, when intermittent, is not marked, and that the enlargement of the kidney is in great measure produced by acute congestion. The polyuria that follows the untwisting of the ureter is due more to an after-secretion of urine than to the discharge of an accumulation in the pelvis. Injurious pressure on neighboring organs by a floating kidney is not common. Sometimes torsion is exerted on the duodenohepatic ligament, leading to compression of the mouth of the common duct, and thus to jaundice. In a case of bilateral floating kidney, Senator observed an aneurysmatic dilatation of the abdominal aorta. This was perhaps due to traction through the renal arteries.

As a rule the function of the floating kidney is not disturbed.

In some cases of floating kidney the stomach is also displaced downward. This has been ascribed to a dragging by the kidney through the duodenorenal ligament, but it is more probable that the descent of the stomach is dependent upon an acquired or a congenital laxness of the gastric ligaments. Very frequently the transverse colon is also displaced downward, and the uterus and its adnexa are unduly movable (enteroptosis, gastroptosis, splanchnoptosis, Glénard's disease).

A curious observation was made by Habel,¹ who found movable kidney

¹ *Centralbl. f. innere Med.*, xviii., 161, 1897.

more frequent in women suffering from *tabes dorsalis* than in other female patients.

Hypertrophy and Atrophy.—Hypertrophy.—Congenital absence or hypoplasia of one kidney is, as a rule, attended by hypertrophy of the other organ. Destruction by disease or extirpation of one organ also leads to hypertrophy of the other kidney, the degree of hypertrophy in this case depending upon the age of the patient. True, or compensatory, hypertrophy affects all parts of the kidney—the cortex as well as the medulla. In growing animals and human beings there is a distinct hyperplasia, or numerical hypertrophy, as well as an increase in size of the individual elements; while the hypertrophy following disease or extirpation of one kidney in adults is generally simple. In true hypertrophy the diameter of the Malpighian bodies, which normally is from 130 to 220 μ , is decidedly

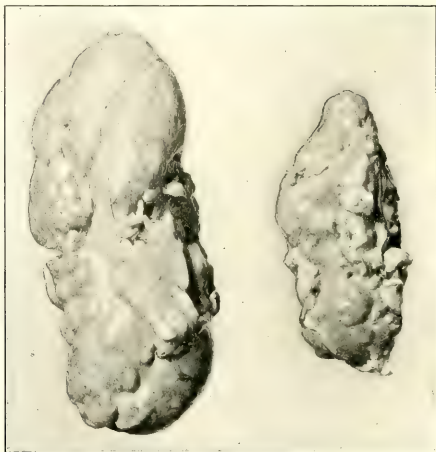


FIG. 500.—Asymmetric kidneys.

increased. The convoluted tubes become wider, up to 90 μ , (normally from 38 to 42 μ).

The normal measurements of other sections of the urinary tubules are as follows: Henle's tubules, descending limb, 9–15 μ ; ascending limb, 25 μ ; papillary ducts, 100 μ and over.

In persons with diabetes mellitus and diabetes insipidus, and in beer-drinkers, the kidneys are often increased in size, and are said to be hypertrophied; but it is probable that the enlargement is largely due to pathologic processes, although a certain degree of true hypertrophy may occur. In diabetes mellitus, for example, the epithelium of the convoluted tubules and glomeruli is often the seat of fatty degeneration, while that of Henle's loop may contain deposits of glycogen. Hypertrophy of the kidney also occurs in acromegaly.

Localized hypertrophy is not rare in the neighborhood of diseased areas, particularly in chronic nephritis of the interstitial variety. Individual

glomeruli may become materially enlarged and the caliber of the convoluted tubules increased in size.

Enlargement of the kidney, not of the nature of true hypertrophy, is seen in acute inflammations, congestion, new growths, and cystic disease. These conditions will be subsequently considered.

Atrophy.—Smallness of one kidney may be congenital (hypoplasia), as has been mentioned. Atrophy of both organs is a frequent senile change. Microscopically the glomeruli and the convoluted tubules are especially affected. The epithelial cells of the latter are reduced in height, lose their striation, and their nuclei stain more intensely than normally. Often the cells are detached from the walls of the collapsed tubules. In fibroid disease of the blood-vessels—arteriosclerosis—and chronic conditions affecting principally the connective-tissue framework of the kidney, the organ is reduced in size. Sometimes in diseased states of the kidney one organ is markedly atrophied, while the other is more nearly normal in size or enlarged. It is at times difficult to explain this asymmetry. In some cases embolic processes affecting one organ, in others, gummata that have healed, are responsible for the unequal shrinkage.

Disturbances of the Circulation.—As in other glandular organs, we find that the amount of blood in the kidney is subject to marked variations. The circulation in the kidney is under the influence of the vasomotor system, but the nerves that accompany the renal vessels are small. They are derived from the renal plexus and the lesser splanchnic nerves, particularly the latter. Stimulation of the peripheral end of the cut splanchnic nerve in an animal causes a diminution in the amount of blood flowing from the renal vein. The blood-vessels of the kidney are plentiful, and their distribution in the organ is such that the blood-supply of the medulla is in a large measure independent of that of the cortex; and disturbances in the one need not materially affect the other. Whether the kidney possesses secretory nerves independent of the vasomotor nerves is still undecided. Stricker was of the opinion that secretion was entirely under the influence of blood-pressure, it being excited by active hyperemia and diminished by the opposite condition. It has, however, been shown by Azoulay and Berkeley that nerves penetrate the *membrana propria* to reach the epithelial cells, on the surface of which they are said to end in knob-like thickenings (Szymonowicz); and Vinci¹ claims to have demonstrated the existence of a secretory center in the spinal cord, the exact location of which is still to be determined.

Anemia.—Anemia of the kidney is met with in cases of profound general anemia from hemorrhage, pernicious anemia, etc. An intense anemia may be caused by obstruction of the renal artery, as by embolism, or through pressure upon the vessel by tumors or fibrous bands. Thrombosis of the artery from disease of the intima may likewise lead to anemia.

Anemia is also said to be produced by a spasmodic contraction of the renal arteries through stimulation, direct or reflex, of the vasoconstrictor nerves. This form of anemia is believed to occur in hysteria, and to it is ascribed the oliguria or anuria common in that disease. The anuria that sometimes follows catheterization and other forms of irritation of the urinary tract may also be attributed to a neurotonic spasm of the renal arteries. Anemia of the kidney is occasionally seen in death from strychnin poisoning, epilepsy,

¹ Congrès de Paris, 1900, *Rev. neurol.*, xi., 350, 1901.

lead-colic, and puerperal eclampsia, and in these conditions is attributed to a general spasm of the arteries.

The consequences of anemia vary with the duration of the condition and the suddenness of its onset. In cases of short duration the kidney is somewhat paler, smaller, and harder than normal. In chronic anemia fatty degeneration of the epithelium is a common lesion. The anemia following obstruction of the renal artery or its branches leads to complete necrosis, if the occlusion is total; or to various degenerative changes of milder degree, if it is partial. This subject will be further discussed under Anemic Infarction.

As the secretion of urine, as already pointed out, depends upon the blood-pressure in the kidney, it naturally follows that in anemia the quantity is reduced. Albumin frequently appears, probably by reason of degenerative changes in the glomeruli.

Hyperemia.—Hyperemia of the kidney may be active or passive.

Active hyperemia or active congestion of the kidney depends, as a rule, upon paralysis of the vasoconstrictor nerves of the renal arteries; perhaps, also, upon stimulation of the vasodilators. Experimentally it can be induced by ligation of the aorta below the origin of the renal arteries, and by division of the renal or the splanchnic nerves. The chief effect of such a hyperemia is increased secretion of urine. When the splanchnic nerves on the two sides are divided, both kidneys become hyperemic, but under these circumstances there is a diminution or a total cessation of urinary secretion. This is explained by the fact that division of the two splanchnics causes paralysis of nearly all the abdominal blood-vessels, and a consequent lowering of the pressure in the aorta to such an extent that the blood flows more slowly through the kidney.

Clinically, active hyperemia occurs: (a) in acute inflammation of the kidney; (b) in the remaining kidney after the fellow-organ has been removed; (c) in diabetes mellitus and diabetes insipidus; (d) in conditions of heightened arterial pressure.

Pathologic Anatomy.—The kidney in active hyperemia is enlarged and firm; the capsule strips easily, and the surface of section is reddish brown, the cortex being a little darker than the pyramids. The glomeruli are distinctly visible. Microscopically the intertubular and glomerular capillaries as well as the larger blood-vessels are filled with blood. Minute hemorrhages are often seen, particularly in the capsular space.

It is rare to find uncomplicated active hyperemia on the postmortem table.

Passive Hyperemia or Passive Congestion.—In this the outflow of blood from the renal veins is interfered with, generally by reason of disease of the heart or lung, causing a damming of blood in the veins. Hence, it is encountered in mitral regurgitation and stenosis, in myocardial disease, in pericarditis, and in emphysema. An acute form of passive hyperemia seems to be produced by death from suffocation.

Local causes may also bring about passive hyperemia. Among these may be named: (a) thrombosis of the inferior vena cava above the entrance of the renal veins. Fisher¹ observed the condition in a girl of thirteen, who was suffering from large white kidney. (b) Thrombosis or compression of the renal veins. This may be due to pressure of tumors or cicatricial bands, or to extension of inflammatory disease from the kidney itself;

¹ *Trans. Lond. Path. Soc.*, xlvii., 113.

or to extension of thrombosis from the vena cava. A form of spontaneous thrombosis occurs in cachectic infants suffering from wasting diseases.

In recent cases the kidney is more or less swollen, especially in thickness. The convex border is widened; the color dark; the consistence firmer; and the organ is full of blood. The capsule strips readily; the surface is smooth, and shows prominently the markings of the stellate veins (stars of Verheyen). On section the organ is darker than normal, especially in the medullary portion, the bases of the pyramids being particularly dark and of a bluish hue. The Malpighian bodies are distinctly visible. In cases of thrombosis of the renal veins or of the vena cava the kidney is edematous as well as hyperemic.

The microscopic changes consist of an overfilling of the veins and capillaries, with small hemorrhages scattered through the intertubular tissue. The capsule of Bowman may contain red corpuscles and an albuminous exudate. A few hyaline casts are also seen in the tubules. The epithelial



FIG. 301.—Hemorrhagic infiltration of the kidney of the newborn.

cells may be filled with reddish or yellowish pigment-granules derived from the hemoglobin of the corpuscles.

If the congestion has been long continued, a characteristic change, designated as *cyanotic induration*, develops. The kidney is not materially enlarged, may even be smaller than normal, but is distinctly harder. Its color is dark red, the cortex being paler than the pyramids. The veins show as dark, vertical striæ. The capsule is slightly adherent in places.

The microscope reveals a thickening of the capillaries, of the veins, and sometimes even of the arteries. The glomeruli are but little altered. Here and there one is atrophic. The tubular epithelium is more or less degenerated, and in part is detached from the basement membrane. Areas of round-cell infiltration may be present. In extreme cases the condition may pass into a state of granular kidney (Schmaus and Horn).

In passive congestion the urine is diminished in quantity, is darker in color, and has a high specific gravity (1025 to 1030). The solid constituents are relatively increased. Urates are readily deposited from the urine on standing. Albumin often appears, together with a few hyaline tube-casts,

leukocytes, and red corpuscles in small quantities. The changes in the urine are attributable, in the first place, to the diminished afflux of arterial blood to the Malpighian tufts; and, in the second, to pressure of the dilated veins upon the uriniferous tubules.

Hemorrhage.—Hemorrhages into the kidney substance are generally small, and take place most frequently from the glomerular capillaries. In severe inflammations or in intense congestions the intertubular connective tissue may become infiltrated with blood, which then often penetrates the tubules. The blood that has passed into the capsular space or into the lumen of the tubules is in part eliminated with the urine, in part converted into a reddish-brown granular pigment.



FIG. 302.—Hemorrhagic infiltration of the kidney of the newborn; thrombosis of the renal vein: a, thrombus.

Extensive hemorrhages into the kidney are the result either of traumatism or of infarction (see below). They are occasionally met with in tumors of the kidney. In traumatic hemorrhage the blood may find its way into the pelvis and pass out with the urine, causing hematuria; but if the capsule is lacerated the extravasation occurs into the surrounding tissues. It is then apt to be very extensive, and may be fatal, as the renal tissue, in the absence of muscle, has no special tendency to retraction.

In the newborn, as the result of difficult delivery, large hemorrhages into the kidney as well as into the other organs not rarely occur.¹ In some cases in which there is hemorrhagic infiltration the labor was not difficult. Here the cause is apparently a thrombosis of the renal vein, due to septic infection (see Fig. 302).

Thrombosis and Embolism.—*Thrombosis of the renal vein* has already been mentioned. It leads to congestion of the kidney, and to the formation of small hemorrhages. In experimental ligation of the renal vein in animals certain other phenomena are observed in addition to congestion and hemorrhages, viz., degeneration of the epithelium and gradual atrophy of the entire organ. The tubules disappear long before the glomeruli.

Thrombosis of the Renal Vein in Infants.—Reference has already been made to this as a condition occurring shortly after birth, the result either of traumatism during delivery or of septic infection. But there is another form met with in anemic and cachectic infants, the so-called *marantic thrombosis*. The left renal artery, on account of its longer course across the aorta, is more frequently affected than the right. The thrombosis, as a rule, extends only into the larger branches. The kidney is swollen and edematous, and often presents numerous hemorrhages. Occasionally the hemorrhage is extensive and involves the entire medullary portion of the organ.

Thrombosis of the renal artery or its branches is rare. Its causes are inflammatory and degenerative changes in the arterial walls and surgical ligation. In aneurysm of the abdominal aorta the blood-clot may sometimes extend into the renal artery.

¹ Spencer, *Trans. Obstet. Soc. Lond.*, xxxiii.

Embolism is much more common than thrombosis; and, as the renal arteries are terminal in the sense of Cohnheim, the usual result is an *infarct*. The immediate consequence of the arterial occlusion is anemia of the parts supplied by the obstructed vessel. The anemic infarct, which forms within from twenty-four to thirty-six hours, is cone-shaped or, according to Ribbert,¹ somewhat quadrilateral, of a dull yellowish-white color, like that of Manila paper, firm in consistence, quite dry, and projects slightly above the cut surface of the organ. The base of the infarct is directed toward the periphery, and is usually close to the surface; while the apex may project as far inward as the pyramids. Small infarcts resulting from obstruction of the cortical arteries may lie in the cortex just beneath the capsule. Infarcts vary in size from that of a pin-head to that of a walnut, but are usually from $\frac{1}{2}$ to 1 cm. in breadth and about the same in height. When large branches of the renal artery are plugged, a third or more of the kidney may be involved in the infarction. The infarct is surrounded either by an anemic or by a distinctly hemorrhagic zone.

In the anemic area necrotic changes begin soon after the stoppage of the arterial influx—in the epithelium, within two hours (Litten), and in the connective tissue within from six to eight hours. The changes are a form of *coagulation necrosis*, and primarily affect the tubular epithelium; later the cells of the glomeruli and of the other tissues. The epithelial cells become granular and larger, and their nuclei disappear. When the area is examined under the microscope not a single nucleated epithelial cell may be visible. The necrotic tissue does not stain with the ordinary dyes, but with eosin it assumes a distinctly reddish-pink hue. Sometimes there is a fibrinous exudate in the lumen of the tubules, and in places the epithelial cells are detached. Eventually fatty changes and absorption of the necrotic material occur, while from the periphery new blood-vessels and new connective tissue penetrate the interior, gradually converting the infarct into a scar, in which for some time degenerated glomeruli and tubules may be found, together with granular detritus, a little blood-pigment, and often calcareous deposits. The contraction of the scar leads to a sinking in and puckering of the kidney surface. If the infarcts were numerous, the whole organ becomes diminished in size from the cicatricial contraction—a condition that may be called *embolic contracted kidney*. In other cases the kidney is divided into lobules, and the appearance may then be mistaken for congenital lobulation. The furrows of the latter are, however, more regular and more shallow than in the embolic kidney.

Occlusion of the main renal artery leads to necrosis of the entire organ, excepting small subcapsular areas that are supplied by vessels of the capsule. The kidney diminishes in size and becomes softer and of a dirty-yellow color.

The causes of embolism of the kidney are the same as those leading to embolic obstruction in other organs—verruccose and ulcerative endocarditis, especially of the aortic valve, atheroma, and polypoid thrombi of the aorta, and clots in aortic aneurysm.

Infiltrations and Degenerations.—**Calcareous infiltration** is found in the kidney under various circumstances:

a. In cases of chronic interstitial inflammation. The deposit here occurs in the form of amorphous masses, either in areas of dense fibrous tissue, especially in the region of destroyed glomeruli, or in necrotic epithelial cells.

¹ *Virchow's Archiv*, clv., 201.

b. In the kidneys of old persons, and of others when there is atrophy and absorption of bone (metastatic calcification).

c. In certain forms of poisoning; as with corrosive sublimate, aloin, bismuth, and phosphorus. The calcification in these conditions takes place principally in necrotic epithelial cells.

The calcareous deposits may be microscopic; or they may be visible to the naked eye as grayish-white striæ, running parallel with the collecting tubules of the pyramids; or as minute yellowish-white points on the surface of the kidney. These white points, as Baum¹ has shown, represent in part calcareous glomeruli, chiefly, however, calcified cysts springing from tubules or Malpighian bodies.

In rare instances the apices of the pyramids are encrusted with calcareous plates.

Under the microscope, in sections stained with hematoxylin, the calcified areas are readily distinguished by their peculiar dark-purple, almost black color.

A deposit of *triple phosphates* may occur upon the pyramids of the kidney in cases in which the urine in the pelvis is strongly alkaline from decomposition.

Calcium oxalate may be found in the kidney in the characteristic octahedral forms in cases in which the food contained large amounts of oxalic acid, or when there was a metabolic disturbance favoring the formation of the acid. Macroscopically the deposits are white; they may be distinguished from calcareous infiltration by their insolubility in acetic acid.



FIG. 303.—Kidneys of a newborn infant, showing uric acid infarcts.

Uritic Infiltration.—Deposits of uric acid, or rather of urates (sodium and potassium), occur in the kidney, as well as elsewhere in the body, in gout and in the so-called uric acid diathesis. They appear as yellowish-white lines, chiefly in the cortex; also in the pyramids. Under the microscope they are usually dark, and in the form of irregular plates or amorphous masses. At times the deposits are large enough to constitute little concretions scattered through the kidney substance, from which they can readily be peeled out.

Uric acid and urates are eliminated with the urine; and if they are

¹ *Virchow's Archiv*, clxii., 93.

abundant and meet with organic material, such as degenerated epithelial cells, they are deposited as stones or calculi, primarily in the pelvis of the kidney. The urates may also pass out with the urine as sand or gravel.

Uric-acid infarcts are, in the writer's experience, an almost constant feature in the kidneys of the newborn (see Fig. 303); although Spiegelberg¹ states that they occur in but half of the infants examined. They are best marked after the second or third day, and then continue for a variable length of time. According to Rokitansky, they may be visible from the fourth to the seventy-sixth day.

It was at one time believed that infarcts occurred only in infants which had breathed; and their presence was therefore considered to possess a medicolegal value. Further study has, however, shown that they may be present in stillborn children.

The infarcts appear as glistening, golden or yellowish-red lines, converging toward the apices of the pyramids. The moisture on the surface of section of the kidney has also a glistening appearance, produced by a scattering of the refracting urate particles over the cut surface. The urine in the pelvis contains an abundance of urates, giving it a turbid yet glistening appearance. Under the microscope the infarcts appear as dark granular masses, filling the lumen of the collecting tubules. On the addition of acetic acid they are dissolved, uric acid crystallizing out; at the same time an albuminous framework becomes apparent. The epithelial cells show no change, and the so-called "urate cells" (Ebstein and Nicolaier) are, according to Aschoff, not seen in the human subject.

As a rule the infarcts disappear promptly; if they persist, they may cause irritation of the kidney substance, and by blocking up the tubules may lead to the development of uremic phenomena.

The *cause* of the infarcts is not definitely known. Virchow was of the opinion that the profound change in metabolism following birth led to an increased formation of uric acid; Vierordt attributed their formation to the feebleness of the oxidative processes in the infant; Spiegelberg,² who was able to produce infarcts in puppies by the injection of 0.25 gram of uric acid per kilo of body-weight, found that the oxidative processes in the puppies were not lessened, and rejects Vierordt's theory. Physical causes also play no part, for Spiegelberg found that the urine of newborn infants, despite its content of uric acid, possesses a greater power of dissolving this acid than the urine of adults.

Argyrosis or the deposition of silver, occurs in the kidney in cases of general argyria following the ingestion of large quantities of medicinal preparations of silver, especially the nitrate. In rare cases the constant local application of silver to a mucous membrane—as that of the throat—may produce a general staining with the metal. The silver granules are deposited chiefly in the cortex of the kidney—about the capillaries of the glomeruli, and usually not in the epithelial cells of the capsule.

Biliary Pigmentation.—Pigmentation by bile occurs in cases of jaundice. If the jaundice has been long continued the kidney has a yellowish or olive-green color. The pigment is found in the epithelial cells, particularly of the cortex, and is usually granular, rarely crystalline. The cells are often fatty as well, and sometimes distinctly necrotic. Tube-casts are present, and are more or less bile-stained.

¹ *Archiv f. experimentelle Pathologie u. Pharmacologie*, xli., 6, 1898.

² *Loc. cit.*

In the condition termed *icterus neonatorum* bile-pigment is found in the kidney in large quantities—*bilirubin infaret*. The deposit occurs in the form of rounded masses or rhombic crystals in nearly all parts of the kidney, but especially in the papillæ. Uric acid infarction is frequently combined with this bile pigmentation.

The urine in jaundice is of a golden, reddish-brown, or greenish-brown color, and froths readily. The formed elements in the urine are stained yellow. Hyaline tube-casts of a characteristic yellow color are often present.

Hemoglobin Pigmentation (*Hemoglobin Infaret*).—This occurs in cases of hemoglobinemia and methemoglobinemia and of hemoglobinuria. The causes are those that bring about these conditions, viz., (a) poisons, such as arsenuretted hydrogen (arsine), potassium chlorate, carbolic acid, pyrogallie acid, amyl nitrite, toluylendiamin; (b) infectious diseases, particularly malaria; (c) extensive burns; (d) transfusion of serum or blood from a different species of animal; and (e) exposure to cold, the latter giving rise to the so-called *paroxysmal hemoglobinuria*.

The kidney is enlarged and of a brownish-red color. On section both the pyramids and the cortex are marked by reddish-brown or yellowish striae. Microscopically the pigment is brownish, and in the form of irregular granular masses, frequently aggregated into casts and filling the lumen of the tubules. Sometimes the pigment appears as brownish droplets, which may also coalesce and form urinary cylinders. As a rule the pigment does not contain iron; but under some circumstances it is ferruginous, and belongs to the group of hemosiderins. In that case it gives the iron reaction with potassium ferrocyanid and hydrochloric acid, and with ammonium sulphid. When crystalline, it is a form of hematin, and is free from iron.

The urine in hemoglobinuria is usually bright red, but may be black, and contains albumin in large amounts. The sediment under the microscope is seen to consist of brownish-red granular matter.

Glycogenic Infiltration.—Glycogenic infiltration occurs in the kidney in cases of diabetes mellitus, and involves especially the epithelium of Henle's loop. The affected cells are swollen, and are more or less filled with homogeneous, glistening droplets, which do not, as a rule, coalesce nor destroy the nucleus. The latter is sometimes much enlarged, and has an hydropic or vesicular appearance. If the tissue is preserved in absolute alcohol and sections are afterward stained with iodine, the glycogen droplets assume a brownish-red color. In staining fresh sections, a solution of iodine in gum-arabic (Lugol's solution, 1 part; thick solution of gum-arabic, 100 parts) is advisable, as glycogen is very soluble in water. The iodine test may also be employed for naked-eye demonstration. In tissues that have been in water, and in which the glycogen has therefore been dissolved out, the cells are seen to contain numerous vacuoles.

There are other substances which stain in a manner somewhat similar to that of glycogen. For differentiation it is best to treat the section with saliva—this promptly dissolves glycogen.

Necrosis of the convoluted tubules is often present in association with glycogen infiltration, especially in cases dying suddenly in diabetic coma. The cause of the necrosis is not definitely known, but it appears to be some powerful toxic agent.

Dropsical Infiltration; Hydropic Change; Edema.—This is a common process in acute inflammation of the kidney, and affects both

epithelium and stroma. In the former it produces enlargement and the appearance of vacuoles; in the latter, a loosening of the texture and a widening of the interspaces.

Leukemic Infiltration.—In leukemia the kidney as well as the liver and other organs is often the seat of an enormous accumulation of leukocytes, which are found in the interstitial tissue. The organ is much enlarged, and mottled with grayish-yellow areas. The leukocytic infiltration is usually diffuse, but may be circumscribed in the form of distinct nodes. The variety of leukemia determines the kind of leukocytes that will be found in the kidney. Uric acid infarcts sometimes occur in connection with leukemic infiltration.

Cloudy Swelling or Parenchymatous Degeneration.—This is one of



FIG. 304.—Leukemic infiltration of the kidney (from a case of Dr. R. C. Rosenberger's).

the most frequent processes in the kidney. It affects the epithelial cells, especially those of the convoluted tubules. The organ is enlarged; the surface on section is convex, owing to a bulging of the renal tissue, and the two opposing surfaces cannot be brought into complete apposition on that account. The structural markings, both in the cortex and in the pyramids, are much obscured, and the surface has a peculiar opaque appearance, so that the organ looks as if it had been cooked. Sometimes there is also considerable hyperemia.

Microscopically the cells of the convoluted tubules are found to be greatly swollen and filled with innumerable fine granules, which in many

of the cells, but not in all, obscure the nucleus; the swelling may be so great that the lumen of the tubules is occluded. The free edges of the cells are usually irregular and often frayed. In advanced stages the cells become detached and lie free in the tubular lumen, or are passed out with the urine. The process has a marked tendency to pass on to fatty change; and, indeed, the two are often seen combined. Cloudy swelling is, however, capable of retrogression, in which case the kidney assumes a more or less normal appearance.

The granules of cloudy swelling are fine; they are soluble in acetic acid, and do not stain black with osmic acid, as do those of fatty degeneration.

The causes of cloudy swelling are, primarily, infectious diseases. Thus, it is found in diphtheria, scarlet fever, cholera, yellow fever, erysipelas, typhoid fever, small-pox, etc. Poisons, such as arsenic, phosphorus, bichlorid of mercury, and mineral acids, may also produce it.

Fatty Changes.—Although in a few animals the renal cells normally contain fat, they do not in man. In cases of lipemia, when the blood is surcharged with fat, it is possible that in its passage from the blood to the urine a little of the fat may be deposited in the renal cells. There is always some fat around the kidney normally. This is increased in obesity; in which condition large quantities are also deposited about the pelvis of the kidney as well. In atrophy of the kidney the fat usually increases *pari passu* with the diminution in the size of the organ.

So-called fatty degeneration is one of the most frequent morbid processes affecting the kidney. It may be localized, occurring in patches; or it may be diffuse. The naked-eye appearance varies with the extent and intensity of the process. When occurring in patches the organ has a mottled appearance; when diffuse the kidney is usually enlarged, and in color varies from grayish yellow to almost butter yellow. The cortex is widened and the striations disappear; the organ has a distinctly greasy feel and leaves an oily stain upon the section knife. In the most extreme cases it is scarcely possible to distinguish between the medulla and the cortex.

Microscopically the parts most affected by the degeneration are the convoluted tubules, but the glomerular epithelium and that of other parts of the tubules may be involved. The cells contain smaller or larger droplets of fat, which have no noteworthy tendency to coalesce. The nucleus is usually invisible. Single cells or the entire lining of a tubule may be detached; often the cells are broken up, and fill the lumen with fatty particles. The latter may be fused into casts. When stained with osmic acid the droplets appear black, and are seen to be of varying size, from a mere speck to a droplet the size of a red blood-corpuscle or larger.

Fatty degeneration accompanies severe acute inflammation, and is a chief characteristic of what is commonly called chronic parenchymatous nephritis. It may be produced by anemia, by the action of the toxins of infectious diseases, by acute yellow atrophy of the liver, and by certain poisons, such as antimony, arsenic, iodoform, chloroform, phosphorus, aloin, and chromic acid; experimentally also by pulegium oil.

Amyloid Degeneration.—Amyloid degeneration is found in the kidney usually as a companion process to amyloid degeneration of other organs, particularly the liver and the spleen; but it occurs also apparently independently in advanced chronic inflammation of the organ, especially in the so-called granular kidney. In the typical form of amyloid degeneration the

kidney is greatly enlarged, is increased in consistence, and has a rather tough, elastic feel; its color is pale grayish yellow, and somewhat translucent, like bacon. On section the striations are generally obliterated; frequently, however, the cortex is marked by reddish hemorrhagic lines. As a rule the pyramids are less affected than the cortex. The iodine test serves to bring out the amyloid areas as dark-brown patches.

Amyloid degeneration primarily attacks the glomerular blood-vessels, and occurs first as minute, homogeneous, paraffin-like masses, that often have a somewhat scalloped outline. Later, through coalescence of the areas, the whole glomerulus may become converted into a homogeneous anuclear disk of amyloid material; the walls of the intertubular capillaries, arterioles, and veins are also affected; and in very advanced cases the membrana propria of the tubules becomes amyloid. Through this change the walls of the vessels and of the tubules become greatly thickened, while the glomeruli are much enlarged. Casts are frequently found in the tubules; whether they are amyloid or hyaline is still in dispute. Their waxy and yellowish appearance is strongly suggestive of an amyloid nature. Amyloid degeneration is often accompanied by the signs of inflammation, and by fatty changes of the epithelium.

For microscopic purposes the iodine or gentian-violet test is useful in demonstrating the extent of the amyloid degeneration.

The causes of amyloid degeneration are primarily prolonged suppuration, such as occurs in tuberculosis and sometimes in syphilis; chronic malaria and other cachectic conditions may also bring about the degeneration. Empyema, bronchiectasis, pyelonephritis, localized suppurative peritonitis, actinomycosis, and gout may lead to the formation of amyloid material in the kidney.

Litten found tuberculosis of the lungs in 70 per cent. of cases of amyloid degeneration of the kidney; in 31 per cent. of these there were also tuberculous ulcers of the intestine. Among Rosenstein's 43 cases of amyloid disease, 17 were associated with ulcerative phthisis, and more than half of the latter were complicated with intestinal tuberculosis. The belief has been held by some that the development of amyloid disease retards the spread of a pulmonary tuberculosis.

The Urine in Amyloid Degeneration.—In the majority of cases of pure amyloid disease the quantity of urine is increased, the specific gravity being lessened. The color is pale yellow. Albumin is, as a rule, present in large quantities (from 0.4 to 0.8 per cent.). In addition to serum-albumin, paraglobulin may be found. In rare cases albumin is absent. The sediment is scanty, and contains a few hyaline tube-casts and leukocytes. When the disease is combined with fatty degeneration of the epithelium (the large white amyloid kidney), the quantity of urine is either normal or diminished, the specific gravity being high; the amount of albumin is very great (up to 3 per cent. or more). The sediment contains leukocytes, often red corpuscles, fatty epithelial cells, and tube-casts of all sorts, including hyaline, granular, fatty, and waxy casts. When the amyloid process occurs in granular kidney, the change usually manifests itself by the presence of a large amount of albumin in a urine of low specific gravity.

Hyaline Degeneration.—Hyaline degeneration is probably closely allied to amyloid change, and, indeed, may be an antecedent of the latter. Both are often associated in the kidney. Hyaline change occurs especially in the glomeruli, and is frequently found in chronic interstitial nephritis. Sometimes the hyaline change affects only one or a few capillary loops of a glomerulus—the degenerated portions then appear as broad, shining, homo-

geneous masses, staining pinkish with eosin, and are without lumen and without nuclei. Calcareous infiltration is apt to take place in such hyaline areas.

INFLAMMATIONS OF THE KIDNEY.

Nephritis.—Owing to the fact that the kidneys are the chief emunctories of the body, the task falls upon them of removing, in addition to the normal waste products, abnormal substances introduced from without or developed within the body. In the performance of this duty they frequently suffer functional and organic changes. The kidneys are, as it were, at the mercy of the circulating blood, which brings to them for elimination substances that may seriously damage the renal cells or the blood-vessels. They have in turn, however, the power of exercising an influence upon the blood constitution. By the elimination of water they alter the composition of the blood; and if they are diseased and the power of removing waste products is impaired, the retention of the latter will greatly modify the state of the blood. The blood thus altered may in turn irritate the kidney, the disease process being continued and intensified. There is thus established a vicious circle which, if not broken, leads to the death of the individual.

Historical.—The ancients had very primitive ideas concerning diseases of the kidney. Hippocrates (460–377 B. C.) was acquainted only with sup-puration. Ætius (died 367 A. D.) and Avicenna (980–1037) recognized the relation between certain kidney affections and dropsy. An important step in the history of renal pathology was the discovery of the presence of albumin in the urine by Cotugno (1736–1822) in 1770. But the era of real knowledge was inaugurated by Richard Bright (1789–1858), of Guy's Hospital, who, in his *Report of Medical Cases*, published in 1827, and in articles in *Guy's Hospital Reports* of 1836 and 1840, laid the foundations upon which all subsequent work in diseases of the kidney is based. He brought the clinical symptoms and the urinary changes into relation with the morbid anatomy of the kidneys, and it has been customary since his day to speak of nonsuppurative inflammations of the kidney as Bright's disease.

Bright's observations were confirmed and expanded by his English contemporaries, by Rayer in France, and by Reinhard, Frerichs, and others in Germany. Rokitansky, in 1842, described the amyloid kidney. Important additions to the clinical history and the pathology of kidney inflammations were also made by Wilks, Johnson, Dickinson, Grainger Stewart, and Gull and Sutton in Great Britain; and by Virchow, Cohnheim, Klebs, Bartels, and Weigert in Germany. Within recent years the studies of Rosenstein, Senator, von Kahlden, Councilman, and Delafield have greatly increased our knowledge of renal diseases.

But despite these extensive labors, diseases of the kidney still remain perhaps the most obscure field in pathology; and there is no unanimity whatever regarding the method of their classification. The same clinical picture may be produced by different forms of kidney disease, and there is often the greatest disproportion between the severity of the symptoms and the renal changes. At the autopsy table it is a frequent experience to find advanced renal disease in cases in which there were few renal symptoms; and severe clinical manifestations, apparently referable to the kidney, may exist with almost normal kidneys.

With Delafield, we may recognize three means of classifying diseases of the kidney: the etiologic, the topographic, and the anatomic.

A classification based upon causes is at present impossible. The reason for this is that widely different causes may produce the same kidney lesions, manifesting themselves by similar clinical and anatomic changes; on the other hand, the same cause is capable of giving rise to more than one type of kidney lesion; thus, scarlet fever may produce at least three forms of renal disease, differing among themselves both clinically and anatomically. The principal causes of disease of the kidney are noxious substances circulating in the blood. These substances may differ qualitatively, and yet produce the same structural changes; while the same cause may, in different individuals, produce different conditions, by its presence in varying quantities.

A classification based upon the part of the kidney involved is both theoretically and practically possible. We may readily distinguish changes in the epithelial structure, the glomeruli, the blood-vessels, and the connective-tissue stroma. This is the basis adopted by most writers upon diseases of the kidney. On this basis we have the following classification: 1. Parenchymatous nephritis, which may be acute or chronic, according to the intensity and duration of the process. 2. Glomerulonephritis, which may likewise be acute or chronic. 3. Interstitial nephritis, of which there are also two types, the acute and the chronic. 4. The arteriosclerotic kidney (Ziegler), in which the changes are principally in the blood-vessels. The flaw in this classification is that it is impossible to draw hard-and-fast lines between parenchymatous and interstitial inflammations. By making due allowance for this, which is feasible, the topographic classification becomes the most practical in the present state of our knowledge, and is the one which, with slight modification, will be adopted in this article.

The last basis is the anatomic. In this the classification is founded upon the nature of the morbid process in the kidney. There is really no marked difference between this and the preceding method of classification, as the nature of the morbid process is governed to a great extent by the part of the organ affected. In this classification, which is adopted by Delafield,¹ diseases of the kidney are divided into congestion, degeneration, and inflammation. The last is subdivided into acute exudative nephritis, acute productive nephritis, chronic nephritis with exudation, chronic nephritis without exudation, and suppurative nephritis.

Ziegler recognizes the following varieties: Acute parenchymatous nephritis, acute suppurative nephritis, subacute and chronic parenchymatous nephritis (and under this head, chronic glomerular nephritis), indurative nephritis, and the arteriosclerotic kidney.

A practical classification, based upon clinico-anatomic considerations, is that of Senator.² He distinguishes:

I. Acute nephritis: (a) Parenchymatous nephritis (tubular and glomerular nephritis); (b) Diffuse nephritis.

II. Chronic diffuse nephritis without induration (chronic parenchymatous nephritis).

III. Chronic indurative nephritis: (a) Secondary induration; (b) Pri-

¹ *Twentieth Century Practice*, vol. i.

² "Die Erkrankungen der Nieren," *Nothnagel's spezielle Pathologie u. Therapie*, Bd. xix., Th. I., 159.

mary indurative nephritis (chronic interstitial nephritis); (c) Arteriosclerotic induration.

Birch-Hirschfeld¹ divides inflammations of the kidney as follows :

I. Acute and subacute nephritis : (a) Acute catarrhal or desquamative nephritis ; (b) Acute glomerulonephritis ; (c) Acute diffuse parenchymatous nephritis ; (d) Acute and subacute hemorrhagic nephritis.

II. Chronic nephritis : (a) Diffuse chronic nephritis with enlargement ; (b) Granular atrophy of the kidney—(1) Secondary contraction of the kidney, (2) Genuine contracted kidney.

III. Suppurative nephritis.

The most recent authoritative classification is that of Councilman,² who recognizes the following varieties of inflammation of the kidney :

I. Acute diffuse nephritis : (a) Acute degenerative nephritis ; (b) Acute glomerulonephritis ; (c) Acute hemorrhagic nephritis ; (d) Acute interstitial nonsuppurative nephritis.

II. Subacute glomerulonephritis.

III. Chronic diffuse nephritis : (a) Chronic glomerulonephritis ; (b) Chronic arteriosclerotic nephritis ; (c) Chronic degenerative and interstitial nephritis ; (d) Senile nephritis ; (e) Amyloid nephritis.

The differences in classification and nomenclature presented by the lists above given, although not very great, nevertheless afford an indication of the difficulties attending the task of classifying inflammatory kidney lesions in a manner that will do justice to the demands of clinical medicine and of pathology. The writer trusts that the following classification may satisfy these demands :

I. Acute nephritis : (a) Acute parenchymatous or degenerative nephritis ; (b) Acute diffuse nephritis—(1) Acute glomerulonephritis, (2) Acute interstitial nonsuppurative nephritis ; (c) Suppurative nephritis—(1) Suppurative pyelonephritis, (2) Embolic suppurative nephritis, (3) Suppurative nephritis through extension from the capsule.

II. Chronic nephritis : (a) Chronic diffuse nephritis without induration (chronic glomerulonephritis) ; (b) Chronic diffuse nephritis with induration—(1) Secondary chronic interstitial nephritis, (2) Primary chronic interstitial nephritis, (3) Chronic arteriosclerotic nephritis ; (c) Amyloid kidney.

Acute Parenchymatous or Degenerative Nephritis (Synonyms : *Acute Tubular or Tubal Nephritis ; Desquamative Nephritis ; Catarrhal or Croupous Nephritis ; Acute Bright's Disease*).—Strictly speaking, this should not be considered an inflammation, as the vascular phenomena characteristic of the latter are absent. It often passes into the next form, diffuse nephritis, from which it cannot be separated clinically, and only with difficulty at the autopsy table.

The principal characteristic of acute parenchymatous nephritis is degeneration of the parenchyma—cloudy swelling, dropsical change, hyaline and fatty degeneration, and necrosis.

Pathologic Anatomy.—Although at times normal in size, the kidney is usually somewhat enlarged and paler than normally ; the capsule is tense and thin, and strips readily. On section the surface is pale and less translucent than normally, the organ looking as if it had been cooked. The cortex is sometimes marked with reddish striæ or reddish dots ; its width is increased,

¹ *Lehrbuch der pathologischen Anatomie*, Bd. ii., 2te Hälfte, 807 et seq.

² *Med. and Surg. Reports of Boston City Hospital*, 1897.

and it bulges a little, so that the halves of the kidney cannot be brought into complete apposition. The pyramids are usually darker than the cortex. The consistence is diminished and the organ is more friable than normally.

Pathologic Histology.—Microscopically the principal changes are exudation into the capsule of Bowman and degenerative changes in the tubular epithelium. The albuminous exudate into the glomerular space appears as a granular material of varying amount. Many of the glomeruli suffer no recognizable change. The epithelial cells affected are principally those of the convoluted tubules. In mild cases they present cloudy swelling, the features of which have been described (see p. 939). Dropsical change and fatty degeneration are often seen. Here and there karyokinetic figures are discovered, indicating regenerative processes. An albuminous exudation is apt to occur into the tubules; and this, together with detached cells, may be transformed into tube-casts.

The causes of acute parenchymatous degeneration are: Infectious diseases, poisons, anemia, jaundice, and pregnancy. It is probable that nearly every acute infectious disease gives rise to parenchymatous degeneration of the kidney. This may be so mild that it does not manifest itself by any symptoms. If more severe, it gives rise to a slight albuminuria (febrile albuminuria). The immediate cause of the renal changes is probably the toxin of the infectious disease, although the fever itself may be a factor in their production.

The Kidney of Pregnancy.—Pathologists and obstetricians have recognized a peculiar renal change in pregnant women, and have designated it as the kidney of pregnancy. It must be separated from forms of nephritis that existed before the pregnancy, and from the commoner types of acute inflammations of the kidney due to poisons, exposure to cold, infectious diseases, etc., to which pregnant women, like other individuals, are liable. When these two classes of cases are deducted, the instances of the kidney of pregnancy remaining are few in number. The nature of the process is in dispute. Frerichs, Virchow, and Grainger Stewart looked upon the condition as an inflammation; Rosenstein considered it purely degenerative. It is most apt to develop in the second half of pregnancy and in primiparas. Various theories have been advanced to explain its production. The principal ones are: (a) That it is due to increased abdominal and pelvic pressure, exerted especially upon the renal veins (Rosenstein), upon the ureters (Halbertsma), or upon the celiac ganglion, thereby causing a reflex contraction of the renal arteries and a consequent anemia of the kidney. (b) The parasitic theory, that the condition is due to bacterial infection. (c) The auto-intoxication theory, according to which the kidney lesion is due to the elimination of excessive amounts of waste products coming from the maternal and the fetal organisms.

Recovery from the kidney of pregnancy is the rule; in severe cases, however, it leads to eclampsia. The relation between the renal disease and the eclampsia, although usually considered one of cause and effect, is by no means definitely settled, since eclampsia may develop in the absence of any signs of renal change. In some instances, indeed, it seems to be the cause of the albuminuria.

The kidney of pregnancy is usually somewhat enlarged, pale, and of a greenish-yellow color. Microscopically the principal changes are found in the epithelium of the glomeruli and the convoluted tubules. They consist in fatty degeneration, cloudy swelling, and, in severe cases, extensive necrosis. The last is usually not diffuse, but is circumscribed to irregular areas in the cortex. Virchow has pointed out the occurrence of fat-embolism in the glomerular capillaries.

The urine in the kidney of pregnancy is usually diminished in quantity, has a high specific gravity, and contains a large amount of albumin; tube-casts may be present, but are sometimes absent, even when the quantity of albumin is very large.

Acute Diffuse Nephritis.—This is the most frequent type of acute inflammation of the kidney. It is characterized by changes both in the paren-

chyma and in the stroma ; hence the propriety of the term diffuse, which in its present connotation has reference, not to spatial extent or amount of kidney substance affected, but to the simultaneous involvement of the two chief components of the organ—the parenchyma and the supporting tissue.

Etiology.—The causes of acute diffuse nephritis are :

1. *Infectious diseases*, particularly scarlet fever, diphtheria, ulcerative endocarditis, small-pox, yellow fever, cholera, typhus and typhoid fever, erysipelas, pneumonia, measles, and acute articular rheumatism ; in rare instances it is produced by follicular tonsillitis, parotitis, chicken-pox, and syphilis. In these various infections the nephritis is chiefly due to the action of the toxin produced by the parasitic cause of the disease. It should, however, be remembered that the kidney eliminates not only toxins, but also the micro-organisms themselves ; sometimes, as in typhoid fever, in enormous quantities. In their passage through the glomerular and inter-tubular capillaries the bacteria may produce structural changes ; and if they

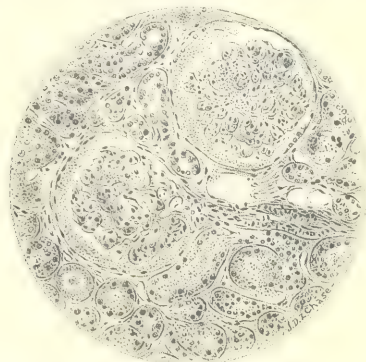


FIG. 305.—Beginning acute diffuse nephritis ; granular exudate into capsular space, which is greatly dilated ; degeneration of tubular epithelium.

metastatically locate in the kidney, as the pyogenic organisms often do, they may bring about striking lesions. Regarding the action of the fever that accompanies infectious diseases, the general opinion is that it plays but a small part in the production of the renal changes, inasmuch as poisons of the class to be considered under the next heading are capable of exciting processes similar to those induced by infectious diseases, without causing any or but slight fever ; hence it is reasonable to ascribe to the infectious toxin the principal role in the causation of the nephritis. It is, moreover, possible to produce experimentally the characteristic renal changes accompanying infectious diseases by injecting toxins, such as the diphtheria toxin, into animals.

A consideration of the physiology of the kidney gives an explanation of the proneness of the organ to suffer from the action of toxins and other poisons. The blood supplied to the tubules first passes, almost in its entirety, through the glomeruli, where it loses water, and possibly certain soluble substances. Through the loss of water it becomes more concen-

trated, so that the toxins act upon the tubules with greater intensity. In addition, the tubular epithelium suffers from the action of whatever toxin may have passed through the glomerular capillaries into the capsule of Bowman, the beginning of the tubule.

Owing to the dependence of the circulation of the tubules upon that of the glomeruli, vascular lesions of the latter exert a profound influence upon the other structures of the kidney.

Certain poisons affect especially the glomerular epithelium; others, that of the tubules. This selective action can be demonstrated by experiment; thus, cantharidin, when injected, produces its chief effects upon the Malpighian bodies, while chromic acid attacks principally the tubular epithelium. This remarkable phenomenon can be better understood when it is recalled that the kidney, as Councilman and Charrin have ingeniously pointed out,

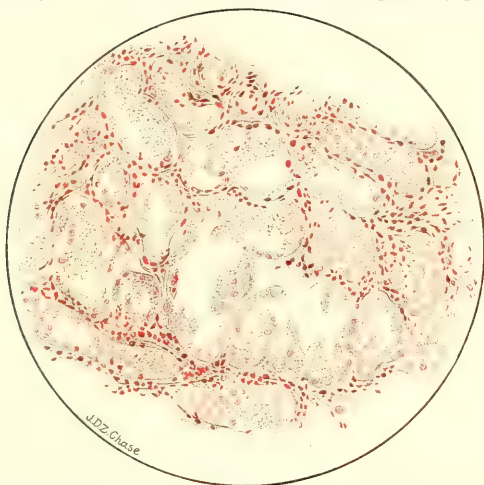


FIG. 306.—Intense subacute diffuse nephritis: degeneration of epithelium; round-cell infiltration of stroma.

is really a double gland. The glomerulus has the structure of a true gland, the tubule being its excretory duct. But this tubule is itself endowed with specific glandular properties, and adds its quota of secretion to that of the glomerulus. It is also probable that the tubule has the power of absorbing certain substances, chiefly water.

2. *Poisons* of various kinds—chiefly of nonbiologic origin—may also cause acute nephritis. The principal of these are corrosive sublimate, carbolic acid, turpentine, cantharides, the chromates, arsenic, ether, chloroform, sulphuric acid, oxalic acid, glycerin, and potassium chlorate.

Substances that bring about methemoglobinemia by destroying red corpuscles (hemolysis) usually cause acute nephritic changes. Of these hemolytic agents, potassium chlorate, already mentioned, is important. Extensive burns also produce methemoglobinemia and, indirectly, renal changes.

3. *Exposure to Cold*.—Pathologists commonly look with skepticism upon this as a cause of nephritis; yet clinically it is at times the only responsible factor. How it acts is not definitely known; there may be a distinct infection, or the exposure to cold or the wetting may alter the composition of the blood—perhaps in a manner analogous to that of the hemolytic poisons—and thus bring about nephritis.

4. *Metabolic Poisons*.—At times acute nephritis develops without apparent cause, although it must be remembered that even a trivial infection, one that is easily overlooked, may be capable of causing nephritis; but there seem to be instances in which the cause must be sought within the body. Leukomains and abnormal proteid substances resulting from perverted metabolism, in the digestive tract or elsewhere, are probably the etiologic factors in these cases.

Pathologic Anatomy.—The appearance of the kidney varies with the duration and intensity of the disease, and the amount of blood present in the kidney at the time of death. The organ is usually enlarged—sometimes to nearly twice the normal size. Both kidneys generally weigh from 400 to 500 grams. In rare instances there is no outward change, either in size or in appearance. In color the organ is, as a rule, grayish white, grayish red, or dark red; often it is mottled with red and white points. The capsule is stretched taut, and strips easily, but may be adherent in a few places. The stellate veins are usually well marked. On section the cortex bulges and becomes convex; it is also wider than normal, and is of a dull grayish-pink or grayish-yellow color. Its striations are indistinct; sometimes it is marked with reddish dots and lines. The Malpighian bodies are often visible as prominent red points. The border or intermediate zone—at the junction of the pyramids and the cortex—is hyperemic and red. The pyramids themselves may be pale, but generally are dark red. The consistency of the kidney is diminished, so that the organ is friable. In more advanced cases the section of surface is mottled by yellowish or grayish-yellow areas; hemorrhagic foci, not disappearing on pressure, may also be present.

Pathologic Histology.—Histologically the changes are seen to affect all the structures of the kidney—the glomeruli, the tubules, and the stroma.

1. *Glomerular Changes*.—To comprehend these, an understanding of the anatomy of the glomerulus is necessary. The glomerulus consists of a tuft of capillary loops not held together by any interstitial tissue. The walls of the capillaries are composed of endothelial cells. Covering the tuft is the inner layer of an invaginated sac—the capsule of Bowman, which is the beginning of the uriniferous tubule. This capsule consists of a double layer: the one covers the capillary vessels, and is known as the glomerular layer; the other, in close contact with it, constitutes the capsular layer. Surrounding the glomerulus is a small amount of connective tissue (periglomerular fibrous tissue). The cells of the capsule are flat, and, although in origin and function epithelial, morphologically resemble endothelium. Some authors therefore look upon the capsule as a miniature serous sac. From this point of view the glomerular layer may be called the visceral, and the capsular, the parietal layer.

The changes in the glomeruli vary greatly: in some cases of acute diffuse nephritis they are slight, or even absent; in the majority, however, they constitute the most striking feature of the kidney; hence the term glomerulonephritis.

It is possible in acute inflammations to differentiate the following changes :

a. Proliferation of the Capillary Endothelial Cells (the Intracapillary Glomerulitis of Welch).—In this the capillaries are dilated and filled with cells possessing a large nucleus and a poorly differentiated protoplasm. A few polymorphonuclear leukocytes and red corpuscles may also be present in the capillaries, together with nuclear detritus and fat-droplets. The protoplasm of the large cells may fuse into irregular masses, or it may take the shape of a reticulum with circular meshes. Hyaline thrombi are often present in the vessels.

b. Proliferative and Degenerative Changes in the Epithelium of the Capsule of Bowman.—In some cases proliferation is very marked—the so-called desquamative glomerulitis—both layers, the capsular and the glomerular, being involved in the proliferative process. The cells in the space may, however, be few in number, because most of them have been washed away



FIG. 307.—Acute glomerulonephritis with exudation. The capillaries are bare of epithelium, and in places are necrotic. There is abundant hemorrhagic and fibrinous exudation in the capsular space, and extending from this into the tubule (Councilman, Mallory, and Pearce).

by the urine, or carried down into the beginning of the tubule, where they may sometimes be seen completely obturating the lumen. The cells coming from the capsular layer are more likely to be detained in the capsule, while those from the glomerular layer are often washed away. Orth explains this on the theory that the former are less directly in the path of the current coming from the glomerular capillaries. The cell accumulation is most marked at a point opposite the entrance of the blood-vessels; therefore, at the beginning of the tubule. A few leukocytes may be present with the other cells in the capsular space. The desquamated epithelium undergoes granular and fatty degeneration. As the result of the desquamation, epithelial defects are often left on the surface of the tuft.

Both the intracapillary and the desquamative glomerulitis are accompanied by an increased permeability of the capillary walls, permitting the exudation of an albuminous urine. It is probable—indeed, likely—that the changes in the glomerular epithelium are also a factor in modifying the

character of the urine secreted. In severe cases a hemorrhagic and fibrinous exudation may occur into the capsular space. In hardened sections the albuminous material is coagulated into a granular mass of crescentic or irregular shape.

It is not possible to separate the two varieties of glomerulitis, although the intracapillary form may occur without any noteworthy changes in the capsular epithelium.

c. Adhesive Glomerulitis (Glomerulitis Adhæsiva).—This change, first described by Engel,¹ occurs particularly in chronic nephritis, but is not confined to it, and may be found in any form or type of renal inflammation. It is characterized by an exudation of fibrin, which passes, in the form of threads, from the inner to the outer layer of the capsule. A prerequisite to the formation of fibrin seems to be degeneration of the glomerular epithelium. The fibrin stage is followed by organization; that is, the development of

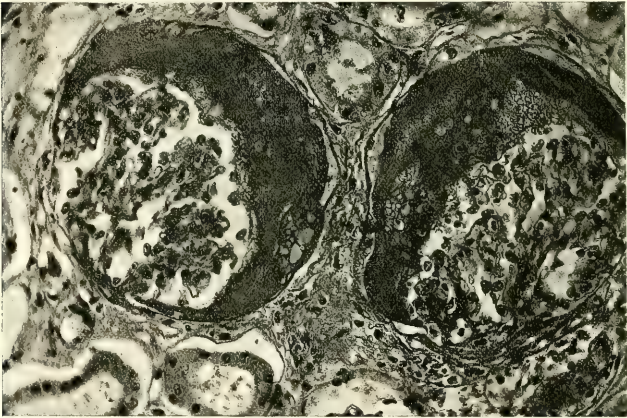


FIG. 308.—Acute glomerulonephritis. In the capsular space is a dense mass composed of red blood-corpuscles and hyaline fibrin. The vascular tufts are necrotic (Councilman, Mallory, and Pearce).

connective tissue. The latter is largely an ingrowth from the periglomerular fibrous tissue, and brings about obliteration of the capsule of Bowman, through which the tubule is rendered functionless. The process, as will be seen, is analogous to an adhesive pericarditis, peritonitis, or pleuritis.

2. *Tubular Changes.*—These are principally degenerative; although with proper staining a few karyokinetic figures, indicating proliferative changes, can be discovered. The degenerations are those already described—cloudy swelling, and fatty, dropsical, and necrotic changes. Not all parts of the tubules are equally affected; the morbid change is, as a rule, most marked in the convoluted portion. In cloudy swelling, as has been mentioned, the cells are swollen and granular; the nuclei indistinct, but generally present; some of the cells are detached. Fatty changes often coexist; also hydropic swelling, manifesting itself in vacuolation of the cells. Necrosis

¹ *Virchow's Archiv*, clxiii., 209, 1901.

is an early change, occurring especially in certain forms of poisoning. The cells are enlarged; the nuclei are not stainable because they have been dissolved (karyolysis), or they are broken up into small chromatin fragments scattered through the cells (karyorrhexis). In rare instances a few epithelial cells from the tubules are forced back through the tubular neck into the glomerulus, between the capillary loops; this anomaly was found by Welch after experimental cantharidin poisoning; and by Councilman in a human kidney.

The lumen of the tubules contains granular detritus, tube-casts, detached cells, hyaline masses, and red blood-corpuscles. In places the lumen of the tubule is dilated and the cells flattened.

In some instances desquamation is a striking feature, the condition, which not rarely affects the collecting tubules, being described as *desquamative nephritis*.

3. *Changes in the Interstitial Tissue.*—These vary in intensity, and are most marked in the acute nephritis of scarlet fever and diphtheria. They consist in exudation of fluid; emigration of leukocytes; diapedesis of red cells, often amounting to distinct hemorrhages; proliferation of the fixed connective-tissue cells; the appearance of a peculiar element—the so-called plasma-cell of Unna; and lastly in alterations in the blood-vessels.

The exudation of fluid produces an edematous swelling of the stroma and a loosening in texture. On account of the swelling the tubules and glomeruli in the affected areas appear more widely apart than normally.

The presence of leukocytes in the stroma is a frequent feature; it is usually confined to the cortex, and the cells are most abundant where the parenchymatous changes are most intense; they may, however, be diffusely scattered throughout the cortex. In some cases the round-cell infiltration is especially noteworthy about the blood-vessels, chiefly the cortical veins. Often there are also distinct cell accumulations about the vessels of the border zone. The leukocytes are small, and, according to Councilman, are generally of the lymphocyte type; but polymorphonuclear cells are likewise present. The cell accumulation is sometimes localized, and so intense as to produce distinct nodules—a condition that has been described by Wagner as *acute lymphomatous nephritis*.

Hemorrhages may be found in the severer types of acute diffuse nephritis—in the glomeruli, in the tubules, and in the stroma. If abundant, the kidney has a distinct red color on naked-eye examination. The red corpuscles usually fuse into a homogeneous, colloid-looking coagulum, staining a brilliant pink or brick color with eosin. Pigment-granules resulting from the altered hemoglobin may also be seen. When the hemorrhagic process is intense the term *acute hemorrhagic nephritis* is appropriate. Extensive hemorrhages may occur with very slight changes in either the parenchyma or the interstitial tissue of the kidney.

Proliferation of the fixed connective-tissue cells is not easily discernible in the acute stages. There is normally, it will be remembered, only a very small amount of stroma in the kidney. The proliferative changes are found especially about the glomeruli and the convoluted tubules. The new cells are large, and have a single pale vesicular nucleus and a nongranular protoplasm. In the subacute and chronic forms of nephritis the stroma is the seat of active proliferative changes.

The plasma-cell of Unna, the occurrence of which in the kidney has been especially studied by Councilman¹ and his pupils, is a large round cell with a large, excentrically placed, well-staining nucleus, having a well-marked chromatin network. Karyokinetic figures are common. The protoplasm is usually abundant, dense, finely granular, and basophilic, staining a deep blue with alkaline methylene-blue. The cells are larger than polymorphonuclear cells, and may be from two to four times the diameter of a red corpuscle. From the epithelial cells, which they somewhat resemble, they may be readily distinguished by the character of the nucleus, which is rather more solid and stains more brightly than that of the epithelial cell. The chromatin network is also coarser than that in the epithelial nucleus. Councilman found these cells principally in the stroma, where they lie loosely in the interspaces. A few are also seen in the blood-vessels. There is no evidence that they are phagocytic. Regarding the origin of these interesting cells, which are found not only in the kidney, but also in many other parts of the body, particularly in the skin, the spleen, and the bone-marrow, it is now generally believed that they are emigrated and altered large uninuclear lymphocytes. They have been seen in the act of emigration, and the shape of many of the cells in the interstitial tissue leaves no doubt as to their ameboid character. It seems that after emigration they may undergo active proliferation by mitotic division.

Blood-vessel changes, apart from hyperemia, are not marked. At times hyaline degeneration of the walls of the capillaries and round-cell infiltration of the adventitia of the larger vessels are encountered.

The changes that have so far been described in detail are combined in acute diffuse nephritis in varying proportions. Ordinarily the parenchymatous alterations are more marked than those in the interstitial tissue. There is, however, a form of the disease in which the cellular exudation in the stroma is the striking feature. On the strength of this marked cellular accumulation, this form has been described as *acute interstitial (nonsuppurative) nephritis*. It was first recognized by Wagner, and has received some attention by the majority of writers since his day. It has recently been very carefully studied by Councilman.²

Acute Interstitial (Nonsuppurative) Nephritis.—*Etiology.*—This form of nephritis is frequently the result of acute infectious diseases, particularly those of childhood. Councilman found it 24 times in 103 cases of diphtheria, and 5 times in 20 cases of scarlet fever; it also occurs in measles, pneumonia, whooping-cough, acute endocarditis, and epidemic cerebrospinal meningitis.

The association of acute interstitial nephritis with acute infections suggests a microbic origin, but bacteriologic examination has, for the most part, proved negative; thus, of 24 cases of diphtheria, 6 were sterile, in 11 the colon bacillus, in 1 the *Staphylococcus aureus*, in 5 the streptococcus, in 8 the diphtheria bacillus, and in 1 the *Bacillus fœtidus*, were found. In 5 cases of scarlet fever the colon bacillus was found in 2, the streptococcus in 3, and the staphylococcus in 1. In 8 cases of mixed infection of diphtheria with scarlet fever or measles, the kidney was sterile in 2, the streptococcus and colon bacillus being found in the others. Not much weight can be given to the presence of the colon bacillus in these cases upon postmortem examination; and as for the other bacteria, they were found in the kidney in the

¹ *Jour. of Exper. Med.*, July and Sept., 1898.

² *Ibid.*, loc. cit.

same proportions in cases in which the lesions of acute interstitial nephritis were absent.

Pathologic Anatomy.—The kidneys are usually normal in size or slightly enlarged. Sometimes they may, even in young children, attain a combined weight that is two or three times the normal. In one case, in a child of two years that had died of the mixed infection of diphtheria and measles, they weighed 480 grams. The capsule is distended and strips easily. The surface of the kidney is pale grayish-opaque, resembles somewhat the amyloid kidney, and is mottled with irregular hyperemic areas. The stellate veins are injected, and often surrounded by small opaque nodules. On section of the kidney the normal markings are obliterated, and the contrast between the medulla and the cortex is obscured. The cortex is greatly increased in width—to three or more times the normal. The glomeruli are

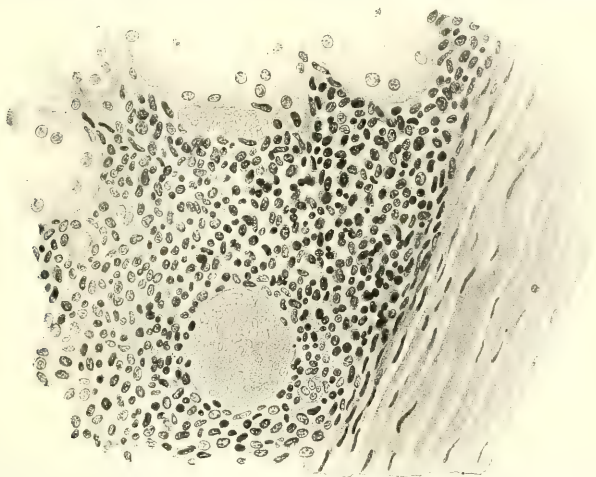


FIG. 309.—Circumscribed focus of interstitial nephritis just beneath the cortex. The large vein in the lower part of the field is a branch of the stellate vein. Zeiss AA, No. 2 ocular. (Councilman.)

not prominent, and usually are invisible. The surface of section is grayish and opaque, and marked with small hyperemic and ecchymotic areas; the pyramids are darker than the cortex. Corresponding with the opaque projections seen on the exterior, areas more opaque than the general cut surface are seen, extending in lines from the pyramids through the cortex. The renal tissue is soft, friable, and moist, and on pressure exudes an opaque, milky fluid. The same fluid may also be scraped from the surface with the knife.

The changes are often most marked at the bases of the pyramids, in the intermediate zone. At times there is a striking discrepancy between the macroscopic and the microscopic changes, the latter often being intense, without a corresponding alteration in the former.

Pathologic Histology.—The changes are best studied in preparations

fixed in Zenker's fluid and stained with eosin and Unna's alkaline methylene-blue.

The seat of the principal changes in acute interstitial nephritis is the *interstitial tissue* or stroma. In this is found an intense cellular infiltration, which, although more or less diffuse, is particularly marked in certain areas: at the bases of the pyramids—the border zone—beneath the capsule, and about the glomeruli. Where the infiltration is intense the cells are crowded together without interval; elsewhere they may lie singly. Independent foci, not connected with the capsular, glomerular, or pyramidal collections, are also scattered through the cortex. In the pyramids the infiltration is usually very intense, and may extend down to the apices.

The cells are identical with Unna's plasma-cells, to the appearances and origin of which reference has already been made (p. 952).

In addition to the plasma-cells, lymphocytes and polymorphonuclear leukocytes are also present, the number of the latter bearing a proportion to the intensity of the degenerative changes in the epithelium. A few epithelioid cells, evidently the offspring of the fixed connective-tissue cells, are likewise seen. The presence of red corpuscles and leukocytes in them testifies to their phagocytic properties.

Changes in the blood-vessels usually accompany the changes in the interstitial tissue. Plasma-cells may be present in such numbers, both within and without the vessels, that the latter are rendered invisible. The intravascular accumulation is most marked in the branches of the small veins in the upper part of the pyramids; occasionally the stellate veins of the cortex present similar collections.

The cells in the interstitial tissue are, in part, emigrants from the blood-vessels; in large part, descendants of these by proliferation.

Tubular Changes.—The tubules are separated by wide areas of interstitial tissue, and their epithelium presents various degrees of degeneration, ranging from cloudy swelling in the mildest cases, to complete necrosis and destruction in the most advanced. Hyaline degeneration is common in the epithelial cells, and appears in the form of small homogeneous droplets. Often the lumen of the tubules is filled with such material. Leukocytes of the polymorphonuclear variety are usually present in the tubular lumen, sometimes in enormous numbers.

Apart from the periglomerular accumulation of plasma-cells, the *glomeruli* show no changes, except in those cases in which a glomerulonephritis is accidentally combined with an acute interstitial nephritis.

The focal character of the interstitial lesions is difficult to explain. It bears no relation to focal degeneration in the epithelium, and is probably connected with irritation of special areas of the kidney by toxic substances contained in the urine. In a large degree, however, physical conditions of the circulation of the kidney are of influence. They particularly govern the accumulation of plasma-cells in the veins of the border zone, and may also be a factor in the cell accumulation in the stellate veins.

Suppurative Nephritis (*Acute Interstitial Nephritis with Suppuration*).—Suppurative nephritis is practically always secondary to similar processes elsewhere in the body. In rare instances it is a result of indirect traumatism to the kidney, the organ becoming a *locus minoris resistentiæ*, and thus a prey to the action of pyogenic organisms, even in the absence of

suppuration elsewhere. The infection in these cases is hematogenic. A penetrating wound of the kidney may become infected directly from without, with the production of suppuration; but this is rare.

Infection in suppurative nephritis reaches the kidney, as a rule, in one of two ways: (a) by the blood (hematogenic, embolic, or metastatic suppurative nephritis); or (b) through the urine which has become infected (urogenic suppurative nephritis).

(a) *Hematogenic Suppurative Nephritis*.—This is due to the conveyance of bacteria to the kidney by the blood-stream, and is therefore an accompaniment of infectious processes localized elsewhere in the body. It is found in general pyemic conditions; in ulcerative endocarditis; in osteomyelitis, diphtheria, scarlet fever, dysentery, small-pox, puerperal infection, bed-sores, pulmonary tuberculosis, and actinomycosis. Some of the latter act by first producing an ulcerative endocarditis, local abscesses, or suppurative thrombophlebitis or thrombo-arteritis.

Orth¹ distinguishes two varieties of hematogenic suppuration: (1) the embolic metastatic, and (2) the simple metastatic. In the former the bacteria are carried to the kidney as distinct emboli; in the latter they do not constitute real emboli or plugs, but are individually detained along the vessel-walls. They then pass out into the surrounding tissue or into the tubules, and multiply there.

The micro-organisms that are capable of producing hematogenic suppurative nephritis are primarily the common pyogenic cocci, then the pneumococcus, and in rare instances the typhoid bacillus and the actinomycetes.

Pathologic Anatomy.—Both kidneys are, as a rule, affected; they are enlarged, and sometimes quite soft. Yellowish-white nodules of variable size and number are visible through the capsule, and represent small metastatic abscesses. They are surrounded by a red areola, and sometimes by distinct hemorrhages. On section, the markings of the cut surface are obscured. The cortex is wider than normally (unless the process has taken place in an organ the seat of chronic nephritis), and both it and the medulla show yellowish areas of suppuration. In the cortex these are more or less circular; in the pyramids they usually follow the course of the tubules. In the pure metastatic (nonembolic) form of Orth the abscesses are located chiefly in the pyramids; hence the designation *mycotic papillary nephritis*.

There may be only a few abscesses, or the kidney may be riddled with them. In size they range from that of a pin-head to that of a hazelnut; rarely they are larger.

Pathologic Histology.—Under the microscope abscesses present themselves as dense collections of polymorphonuclear leukocytes, which invade the interstitial tissue and fill the lumen of the tubules and the capsular space of the glomeruli. Sometimes a partly destroyed glomerulus forms the nucleus of a suppurative focus. It is often possible to find bacterial emboli as the core of abscesses. In sections stained with hematoxylin and eosin the micrococcal embolus stains a pale homogeneous blue, and is surrounded in a concentric manner by a necrotic zone taking a pinkish stain. About this, attracted by chemotactic substances, is the zone of leukocytes. The cells nearest the necrotic zone are more or less degenerated and broken up into fragments and nuclear detritus.

The bacterial emboli may be lodged in the glomerular loops in the

¹ *Lehrbuch der speciellen pathologischen Anatomie*, ii., 62.

peritubular capillaries, or in small arterioles; in rare cases they are found in the capsular space and in the lumen of the convoluted tubules.

Changes of a variable degree of intensity elsewhere in the kidney accompany the abscess formation. There is always destruction of the renal tissue within the confines of the suppurative process; and at a distance we find edema, cloudy swelling, desquamation, and even necrosis.

In suppurative papillary nephritis (nephritis papillaris mycotica) the bacteria are usually found in the tubules of the papillæ and of the median zone of the pyramids. Epithelial cells in the affected area are destroyed. At times hyaline casts are present, about which the bacteria are collected. Sometimes the bacteria themselves are so numerous and compact as to constitute casts. The abscesses show the usual three zones: the bacterial, in the center; the necrotic; and the leukocytic. The presence of bacteria in the collecting tubules is evidence of the nonembolic nature of the process, and indicates that they were, so to say, secreted into the lumen, where they afterwards multiplied.

The changes produced by embolic suppuration of the kidney may be readily demonstrated experimentally by injecting *Staphylococcus aureus* cultures into the ear-vein of rabbits.

(b) *Urogenic suppuration of the kidney* is the most frequent form of renal suppuration. It is brought about by the advent of bacteria to the kidney from the pelvis or lower parts of the urinary tract; hence it is also called *ascending suppurative nephritis*.

Etiology.—Ascending infection of the kidney may be produced by suppurative processes in any part of the urinary tract. The principal causes are as follows:

(1) *Pyelitis*.—Inflammation of the pelvis of the kidney is the most frequent starting point of urogenic infection of that organ. The pyelitis may be due to stone or to tumor, but in the majority of cases it is the result of ascending infection from the bladder.

(2) *Ureteritis*.—As a primary disease, furnishing the starting point of suppuration in the kidney, ureteritis may be brought about by tumors compressing the canal from without or occluding it from within.

(3) *Cystitis*.—This is the most common cause of suppuration in the kidney. It usually brings about the renal infection by first producing a pyelitis. Although the infection ascends along the ureters, the latter may not be greatly altered.

Pathologic Anatomy.—Usually only one kidney is affected, particularly if the condition is due to primary pyelitis. Inflammation ascending from the bladder may, but does not necessarily, give rise to bilateral suppurative nephritis. For evident reasons, the process starts in the pyramids—in the apices of the papillæ—and ascends by way of the tubules until it reaches the cortex, which, as a rule, is less affected than the medulla. The kidney is enlarged, hyperemic, and soft. The abscesses may be small; but by coalescence large pus collections may be produced. In the early stages the abscesses radiate in yellowish-white lines, following the striations of the pyramids; in advanced cases the papillæ melt away; and in extreme examples the greater part of the kidney structure disappears, the organ being converted into a large pus-sac (pyelonephritis). The abscesses may rupture into the renal pelvis; or through the capsule into the perirenal and pararenal tissues, the intestines, the liver, the bronchi, the peritoneum, or even externally. In

some instances the pus becomes encapsulated or absorbed, the acute process terminating in a chronic fibroid change of the kidney.

The ultimate cause of urogenic suppurative nephritis is always bacterial, and recent investigations have shown that the principal organism responsible for the affection is the *Bacillus coli communis*; the *Proteus vulgaris* appears to be next in frequency and importance. The former usually occurs in cases in which the urine is acid, while the latter is found with ammoniacal decomposition of the urine. General systemic infection from pyelonephritis is possible, and leads to the development of pyemia.

Pathologic Histology.—In the early stages the collecting tubules are filled with leukocytes, detritus, and bacteria; as the abscess grows larger necrosis takes place in the surrounding tissue; small foci of round-cell infiltration are also found in the cortex. In long-standing cases the abscesses may be surrounded by a more or less well-defined connective-tissue wall.

Perinephritis and Paranephritis.—These are, as a rule, the result of extension of inflammation from the kidney, but may be due to suppurative processes in the neighborhood or at a distance, in which case the kidney is often secondarily involved. The conditions are found in association with lumbar and psoas abscesses, suppuration of the retroperitoneal glands, empyema, traumatic infections, perforation of the intestine, and pyemia.

Perinephritis is inflammation of the capsule of the kidney; *paranephritis* is inflammation of the fibrofatty tissue in which the kidney is embedded. Paranephritic abscesses are usually large, and may perforate externally in the region of the loin, or into the pleural cavity, intestine (*e. g.*, the duodenum), lung, peritoneum, renal pelvis, vagina, or bladder.

If the pus is absorbed or encapsulated, a chronic fibroid inflammation usually succeeds, and involves the kidney-capsule and pararenal tissue. The kidney is then ensheathed in a thick mass of cartilaginous hardness, to which it is usually adherent. Orth mentions a case in which contraction of the pararenal tissue brought about thrombosis of the renal artery, with consequent total necrosis of the kidney.

Apart from being caused by extension of inflammation from the kidney itself or from the surrounding tissues, perinephritis is also produced by operations upon the organ, such as nephrotomy, nephrorrhaphy, or nephropexy. The inflammation in these cases is naturally localized in character.

The Nature of the Renal Changes in the different Infections and Intoxications.—The lesions produced by infectious diseases and intoxications have now been described from a general standpoint, but it will be well to take up the different diseases separately, and briefly discuss the renal changes produced by them.

Scarlet Fever.—The appearance of the kidney in scarlet fever varies with the stage of the disease. In patients that have died very early the kidney presents very slight macroscopic changes, but microscopically exhibits degeneration of the epithelium of the convoluted tubules. If death has occurred at the height of the disease, the kidney is usually enlarged, flaccid, and either pale or red from hemorrhages and congestion (the flaccid large white kidney and the flaccid large hemorrhagic kidney of Friedländer). The most frequent type of nephritis in scarlet fever is that known as postscarlatinal nephritis; this is, as a rule, a glomerulonephritis. In some cases interstitial changes, such as have been described under the head of acute interstitial nonsuppurative nephritis, are found. Congestion of the vessels and fatty degeneration of the epithelium are present in practically all cases; glomerular lesions are, however, not a necessity, and were absent in a series of cases studied by Pearce.¹

Diphtheria.—There are no characteristic lesions. Degenerative changes in the epithelium are always present, frequently with more or less pronounced alterations in

¹ "Scarlet Fever," *Reports of Boston City Hospital*, Tenth Series, 1899.

the interstitial tissue (accumulations of plasma-cells), and in the glomeruli. Glomerulonephritis is especially common in older children, and in cases of prolonged duration. The lesions are not due to the bacteria, but to the toxic substances in the blood. The diphtheria bacillus may, however, be present in the kidney on culture.

Pneumonia.—There is nothing characteristic in the nephritis of pneumonia. Degenerative changes—cloudy swelling and fatty changes—are found in the epithelium of the convoluted tubules. The glomeruli are usually intact. Hemorrhages are not infrequently present. Although the pneumococcus may be found in the kidney on culture, the renal changes are unquestionably the result of its toxin. The previous existence of renal disease makes a pneumonia more grave; indeed, it usually brings about a fatal termination.

Typhoid Fever.—The kidney is enlarged and congested, and is the seat of punctiform hemorrhages. Cloudy swelling and fatty changes in the convoluted tubules and Henle's loops are present. In rare cases there is a distinct glomerulonephritis. As the typhoid bacillus is eliminated in large quantities by the kidney, it is probable that it can be demonstrated in the organ on culture.

Measles.—Clinically, nephritis is rare in measles. In fatal cases cloudy swelling and fatty change in the epithelium of the tubules are found. The capsular epithelium also shows degeneration, and sometimes desquamative changes.

Chicken-pox.—Nephritis is rare in this disease, but occurs, and is characterized by changes resembling those seen in scarlet fever.

Small-pox.—The kidneys show degenerative changes, especially cloudy swelling. An interesting lesion frequently found is hemorrhagic infiltration of the pararenal fatty tissue, which in a measure may explain the severe pain in the back so constant in variola.

Influenza.—Nephritis is rare in influenza. When it occurs it may present itself as a degenerative nephritis or as a glomerulonephritis, and exceptionally as a hemorrhagic nephritis.

Erysipelas.—Acute nephritis occurs in about 4.7 per cent. of the cases of erysipelas.¹ The streptococcus may be found in the kidney.

Cholera.—The appearance of the kidney in cholera depends upon the stage at which death occurs. In fulminating cases very little macroscopic change is found; microscopically, cloudy swelling and fatty changes in the epithelium of the convoluted tubules are present; at times, also, necrosis of the nuclei of these cells. When death has occurred at a later date the kidney has a violet hue, and if the condition is still more advanced, the color is slightly yellowish. On section the organ has a sticky, glabrous feel; to this considerable importance has been attached as a diagnostic feature. The border zone is hyperemic; the papillæ are pale; the epithelial cells are fatty, and often broken into a granular debris. The convoluted tubules are dilated, and the lumen filled with degenerated cells and detritus. The Malpighian bodies are normal, except for hyperemia, and the stroma is free from cellular infiltration.

The ultimate cause of the renal changes in cholera has been explained in various ways. Some have maintained that the anemia or ischemia produced by the profound depression of the circulation, which manifests itself in absence of the pulse and almost complete suppression of the heart-sounds, is the cause of these changes; others ascribe the nephritis to the cholera-toxin. In all probability both factors are at work, the toxin having the larger share of influence.

Regarding the urinary secretion, complete anuria is a common condition in cholera. In some cases, however, the urine is scanty and contains albumin. The indican and ethereal sulphates are increased; ammonia and acetone are also present in large quantities. The other solids are diminished in amount.

Plague.—Nephritis is common in severe cases, but presents nothing peculiar. The urine contains nucleo-albumin, serum-albumin, and blood; its specific gravity is low; the chlorids are diminished; indican is present; in the sediment granular casts, a few hyaline casts, leukocytes, and red corpuscles are found. The presence of blood is usually due to lesions of the lower parts of the urinary tract. At times the plague bacillus is demonstrable in the urine.

Malaria.—In acute cases there is, as a rule, no macroscopic change in the kidney; sometimes cloudy swelling, hyperemia, and punctiform hemorrhages are present. Under the microscope pigmentation of the glomeruli, and at times of the intertubular capillaries, is found, the pigment being contained in intravascular leukocytes and in endothelial cells. The parasites are rare in the glomerular capillaries, but are common in those of the stroma. There are also degeneration and desquamation of the capsular epithelium, and an albuminous exudate is present in the capsular space. The epithelium of the convoluted tubules is likewise degenerated, and tube-casts are

¹ Lenhartz, Nothnagel's *Specielle Pathologie und Therapie*, Bd. iii., 3. Theil, 55.

abundant. The general appearance of the kidney suggests the action of a toxic rather than that of an organized agent.

Chronic malaria or malarial cachexia gives rise to amyloid disease, which in these cases is especially marked in the kidney.

Malarial Hemoglobinuria.—A few words should be devoted to the changes in the kidney in malarial hemoglobinuria. The kidneys are usually enlarged and congested, and on section present brownish-red or black striæ, particularly in the pyramids. In the most severe cases the kidneys¹ are enlarged, flaccid, edematous, and icteric, with a blackish discoloration of the pyramids and medullary rays. Microscopically the principal change is found in the tubules, the glomeruli presenting no notable alterations. There is no imbibition of hemoglobin by the lining cells of Bowman's capsule, nor any free granules of hemoglobin within the capsular space. The convoluted tubules present cloudy swelling, fatty degeneration, and occasionally distinct necrosis. At times there is an abundant granular detritus without hemoglobin in the lumen of the tubules; other tubules contain hemoglobin casts, and in such tubules the epithelium is usually preserved, although somewhat flattened. Some of the epithelial cells may contain hemoglobin pigment, and at times bile-pigment is present, usually within tube-casts. The casts are generally most numerous in the pyramids. The epithelium of the straight tubules is, as a rule, markedly degenerated. Many of the tubules are dilated, and contain a granular débris, consisting of disintegrated epithelial cells and hemoglobin particles. Evidences of proliferation of the epithelium, in the shape of mitotic figures, are sometimes seen. Except for hyperemia, the stroma presents no alterations worthy of note.

The cause of malarial hemoglobinuria is not definitely known. There is evidently some hemolytic substance (hemolysin) in the blood, which dissolves the red corpuscles; but, according to Marchiafava and Bignami, this hemolysin is not produced by the malarial parasite.

Yellow Fever.—According to Sodré and Couto,² the kidney is normal in size or slightly enlarged. The color is pale yellow, sometimes unaltered. The cut surface shows some hyperemia, the cortex being yellowish or pale. Microscopically there is extensive fatty change of the epithelium of the tubules. In some of the tubules the cells are swollen and encroach upon the lumen, the latter being filled with a compact mass of epithelial débris, free granules, etc. The glomeruli, as a rule, present no alteration, and are conspicuous features, surrounded as they are by diffuse degeneration of the tubular epithelium.

Epidemic Cerebrospinal Meningitis.—There is nothing peculiar in the kidney in this disease. Councilman, Mallory and Wright,³ found only acute degenerative changes in the epithelium. These, however, were always present.

Anthrax.—In anthrax the kidney is hyperemic and friable. There is not much epithelial change. Bacilli are present in varying numbers, and are most abundant in the border zone between the pyramids and the cortex.

Rabies.—In animals (e. g., dogs) there is usually a parenchymatous nephritis. At times the urine contains the infectious agent, and may be used for purposes of inoculation.

The changes in the kidney in the so-called *infectious granulomas* will be considered in a separate section.

Intoxications.—*Potassium Chlorate.*—The kidney is large and brownish yellow. The epithelium of the tubules is degenerated, and the tubular lumen is filled with blood-corpuscles and blood-pigment. There are no noteworthy changes in the interstitial tissue. The urine contains hemoglobin.

Potassium Chromate.—This produces a diffuse nephritis, with predominant involvement of the convoluted tubules and Henle's loops. The cells are destroyed by a coagulation necrosis. The glomeruli generally escape. A moderate amount of albumin is found in the urine.

Oxalic Acid.—The kidney is hyperemic, and the cortex and cut surfaces are marked by whitish lines, indicating deposits of calcium oxalate. The tubules are in part plugged with crystalline masses of plate-like form. The octahedral type of crystal is usually not seen.

Arsenic and Phosphorus.—Both of these produce principally a fatty change in the epithelium.

Mercuric Chlorid.—The kidney is enlarged, soft, whitish-gray, and marked with hemorrhagic and white spots, the latter representing calcareous deposits. Histologi-

¹ Marchiafava and Bignami, *Twentieth Century Practice*, xix., 499.

² Nothnagel's *Specielle Pathologie und Therapie*, Bd. v., 4. Theil, 2. Abth., 123.

³ "Epidemic Cerebrospinal Meningitis, and its Relation to Other Forms of Meningitis," *Report of the State Board of Health of Massachusetts*, 1898, 122.

cally there is an extensive necrosis of the epithelial cells, particularly of the convoluted tubules, with calcification. According to Kaufmann, the calcification affects the epithelial cells; while Klemperer states that the deposit occurs in the tubular lumen. Calcification is usually attributed to anemia of the kidney, produced by the poison.

Cantharides.—This chiefly produces a glomerulonephritis, but the stroma is involved to some extent. The urine contains albumin in large quantities.

Aloin.—The studies of aloin nephritis have been made upon animals. There is a diffuse nephritis, the glomeruli are enlarged, and the capsular space is the seat of a hemorrhagic or albuminous exudate. The convoluted and straight tubules are degenerated, and contain hyaline casts. The stroma changes consist of hyperemia and hemorrhages.

Chronic Nephritis.—The principal characteristic of chronic nephritis is a productive inflammation of the interstitial tissue or stroma. Epithelial changes are always present, sometimes, indeed, in such an intense degree as to overshadow the interstitial inflammation. On the other hand, the latter may be so pronounced that the epithelial alterations are an inconspicuous feature.

The kidney may be larger or smaller than normal, the size depending upon various factors, the principal of these being the degree of hyperemia, the amount of interstitial change, and the presence or absence of amyloid degeneration. In view of this, size becomes to some extent a criterion of the nature of the morbid process in the kidney.

1. *Chronic Diffuse Nephritis, without Induration*.—It is impossible to draw a sharp line between acute and chronic forms of diffuse nephritis. The alterations in the latter are only an intensification of the processes characteristic of the former. The parenchyma presents changes that are principally degenerative, but also some, especially in the glomeruli, that have a proliferative character. The stroma is always the seat of distinct changes, both exudative and proliferative in type. The phrase "without induration" signifies that the new cells of the stroma do not proceed to form mature connective tissue. Hence there is no scar-tissue, no contraction, and no induration.

Naturally, the intensity of the changes depends upon the duration of the disease, and it is not uncommon in advanced cases to find some fibrous-tissue formation in limited areas. The appearances of the kidney, both macroscopic and microscopic, are, moreover, frequently modified by the occurrence of terminal acute lesions, either engrafted as independent processes or constituting exacerbations of the pre-existing inflammation. The occurrence of amyloid degeneration is also very common in chronic forms of nephritis. It has a marked influence both upon the size and upon the appearance of the kidney. In many cases in which the organs are considered at autopsy to be pure examples of chronic diffuse nephritis, the microscope or the iodine-test reveals the existence of amyloid degeneration.

Etiology.—In rare cases chronic diffuse nephritis is the sequel of acute inflammation of the kidney, especially that due to scarlet fever, malaria, erysipelas, or exposure to cold; but in the majority of instances the disease begins insidiously, and is chronic without ever having been acute. The provocative agents in this case are unknown; the infectious diseases, particularly malaria and syphilis, constant exposure to cold and dampness, alcohol, rheumatism, and chronic heart-disease are supposed to play a part. It is possible that the elimination of micro-organisms, in which the kidney is probably engaged not only during the course of acute infections, but also at other times, is a factor in the production of chronic nephritis. There are

many channels through which micro-organisms may enter, even in the absence of acute infectious diseases: through ulcers in the mouth and about the teeth, through the pharynx and the tonsils, through wounds, and perhaps through the mucous membrane of the digestive tract and the genito-urinary tract (urethra, vagina, and uterus). The organisms most concerned are, we may assume, the pyogenic cocci and the *Bacillus coli communis*.

Metabolic poisons, elaborated in the digestive tract or in the interior of organs or muscles, are presumably a factor in the causation of some cases of chronic nephritis. It has been shown by Hughes and Carter¹ that the blood-serum of patients suffering from Bright's disease contains something capable of producing nephritis in animals injected with it.

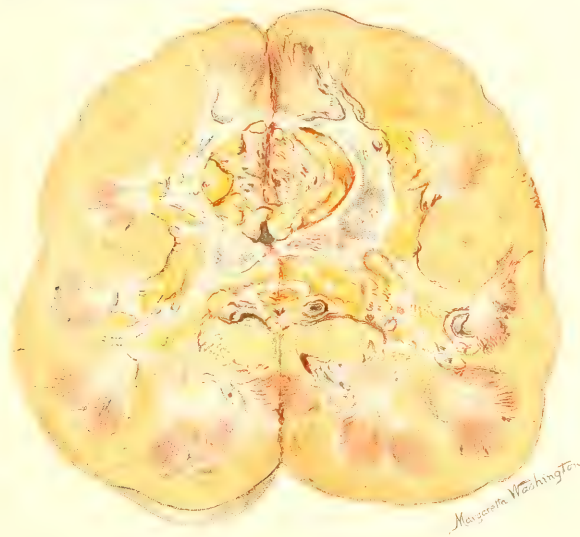


FIG. 310.—Large white kidney.

Chronic diffuse nephritis occurs especially in men, between the ages of twenty and forty; but it is also met with in women and in children.

Pathologic Anatomy.—The naked-eye appearance of the kidney is variable. The organ is usually enlarged, sometimes to almost twice its normal size. Its consistence is generally diminished; the larger the kidney, the softer, as a rule, is its consistence. The capsule is stretched tightly, but strips with ease, although at times small bits of the cortex are brought with it. The color is either yellow or red, according to the amount of blood and the degree of fatty change. When the yellow color predominates, the kidney is often described as the *large white kidney* or the *large yellow kidney* (*chronic parenchymatous nephritis*). The surface is smooth, grayish-yellow or butter-yellow, sometimes mottled with whitish and deep yellow

¹ *Am. Jour. Med. Sci.*, viii., 177, 268, 1894.

patches. The superficial veins are conspicuous. The kidney is very flaccid, soft, and almost doughy. On section the cortex is seen to be increased in width, and to have a yellowish or mottled color. The medullary rays may have a grayish, translucent appearance, which contrasts with the deep yellow of the labyrinth. As a rule, the pyramids are darker than the cortex; sometimes, however, the cortex and medulla are uniformly yellow. The surface has a somewhat oily feel, and the section knife is stained with oil-droplets.

The appearance of the kidney is often modified by the presence of congestion and hemorrhages, these giving rise to the so-called *chronic hemorrhagic nephritis*, or the *large mottled kidney*. The organ in this form is of normal size or slightly enlarged; its consistence is somewhat increased. Here and there the capsule is adherent. On the surface grayish or yellowish and reddish areas alternate, giving the kidney a distinctly variegated appearance. The cortex on section is found widened, and marked with reddish striae or reddish patches of hemorrhage.

Pathologic Histology.—The microscopic changes involve the glomeruli, the tubules, and the stroma. The principal characteristic in all is a fatty change in the epithelium. It is this which, together with anemia, gives rise to the pale color of the organ.

Glomerular Changes.—These are always present, and are both of a degenerative and a proliferative character. The degeneration—usually hyaline or fatty—attacks the epithelium of the capsule and the capillary endothelium, and may cause almost complete disintegration of the affected glomeruli. The proliferative changes manifest themselves in proliferation and desquamation of the capsular epithelium, the affected glomeruli then appearing highly cellular. Sometimes the proliferated cells arrange themselves about the capillary tuft in crescentic and semicircular masses. In addition to the epithelial cells, the capillary space may contain a granular detritus, leukocytes, and blood. The capillaries are often filled with hyaline thrombi.

Sometimes the features of adhesive glomerulitis, described on page 950, are found. The connective-tissue ingrowth may be associated with proliferation of the capsular epithelium. As a rule, the result is obliteration of the capsular space and destruction, so far as functional purposes are concerned, of the glomerulus.

In a large number of cases the glomerular changes are very marked, those in the tubules being subordinate. To such forms the terms *chronic glomerulonephritis* is applicable. In hemorrhagic nephritis there is an abundant exudate of blood into the capsular spaces.

Tubular Changes.—The most prominent feature is fatty change in the epithelium, especially in that of the convoluted tubules; in advanced cases the epithelium of the straight tubules may also be involved. The fatty cells are enlarged, and may preserve their general shape; sometimes they are detached and disintegrated into finer or coarser granules. Usually not all of the cortical tubules are affected, the degeneration tending to be focal in character. The lumen of the tubules is often dilated, and contains granular matter, fatty and hyaline droplets, and hyaline tube-casts. The epithelium of the dilated tubules is greatly flattened. In hemorrhagic nephritis the tubules contain red blood-corpuscles, which may be distinct and separate, or may be fused into homogeneous colloid masses. Altered blood-pigment is present in the epithelial cells and in the interstitial tissue.

Changes in the Interstitial Tissue.—These are ordinarily not very marked. They consist in edema and small foci of round-cell infiltration about the glomeruli and veins. Fat-granules, as well as blood-pigment, are present in the stroma, in the hemorrhagic form of chronic diffuse nephritis. In some cases there is a distinct cellular proliferation about the glomeruli and tubules. The endothelium of the blood-vessels, especially that of the tufts, shows fatty changes.

In hemorrhagic nephritis, or the large mottled kidney, to which reference has several times been made, the histologic features are, on the whole, similar to those of the large white kidney; but fatty changes are less pronounced, and there is an infiltration of blood into the glomerular spaces, the tubules, and the interstitial tissue. The affected tubules are often destroyed, the epithelium being lost. The blood may form tube-casts. There is a more marked tendency toward the production of new fibrous tissue, and this leads to the destruction of many glomeruli and tubules. Foci of round-cell infiltration are also present.

Chronic Diffuse Nephritis with Induration (*Chronic Interstitial Nephritis*).—The meaning of this term has already been indicated in the definition of chronic diffuse nephritis without induration. There are several forms, which are described below.

(a) *Secondary Chronic Interstitial Nephritis.*—Reference has just been made to the fact that in chronic diffuse nephritis without induration there are evidences of connective-tissue proliferation. If the disease lasts for some time this connective-tissue overgrowth becomes more marked, and gives rise to an increased consistence of the kidney, and not infrequently to a reduction in size. It must be evident that no sharp line can be drawn between chronic diffuse nephritis without induration and this form of chronic interstitial nephritis. All possible intermediate stages may be found, and even the chasm between it and acute nephritis is bridged by subacute forms of inflammation.

The secondary chronic interstitial nephritis is the most frequent type of chronic renal disease, and, as we have indicated, is an advanced stage of the chronic diffuse nephritis without induration. It is more often secondary to the so-called large mottled kidney than to the large white kidney, because the patient with the latter does not survive long enough to give an opportunity for much connective-tissue growth. However, if the disease lasts any length of time, some newly formed fibrous tissue will invariably be found.

Pathologic Anatomy.—The organ may be normal in size, larger or smaller, its bulk depending upon the duration of the disease and the degree of filling of the blood-vessels. The capsule strips easily, except in a few places where it adheres to the cortex. The surface may be smooth or slightly granular, and cysts are not rarely present. The color is dark red or mottled, or grayish-yellow. The consistence is increased. On section the cortex varies in width; it may be wider than normal, but in places is often greatly reduced. It is opaque and mottled, grayish-yellow patches of degenerated parenchyma alternating with reddish areas.

Pathologic Histology.—The principal alteration is in the cortex, the glomeruli being especially affected. There is hyaline degeneration of isolated capillary loops, or the entire glomerulus may be converted into an anuclear hyaline ball. Many of the glomeruli are surrounded by a thickened fibrous capsule, from which there may be an ingrowth into the interior,

causing obliteration of the capsular spaces, as has been described under Adhesive Glomerulitis. Not all the glomeruli are destroyed, however, and many of those that escape are larger than normal, apparently as the result of compensatory hypertrophy. The tubules are more or less degenerated and atrophied; some are entirely destroyed, their places being taken by a homogeneous connective tissue; others are dilated into cysts. Tube-casts may be present. The stroma is increased in width by round-cell infiltration and newly formed connective tissue. The interstitial changes are secondary to the degeneration in the parenchyma.

(b) *Primary Chronic Interstitial Nephritis*.—This, also known as gouty kidney, granular kidney, red granular kidney, or contracted kidney, develops insidiously, without evidences of preceding inflammation of the kidney. Anatomically it is not easily separated from advanced stages of secondary interstitial nephritis; clinically it is characterized by the fact that, no matter when the first symptoms are discovered, they are already those pertaining to a chronic nephritis. Sometimes a history of an acute infectious disease early in life is obtained, and it is possible that the damage suffered by the kidney at that time prepared the way for the ultimate development of the chronic interstitial inflammation; however, in the majority of cases no such antecedent condition exists, and the disease is to all intents and purposes a primary chronic process.

Etiology.—The etiology is obscure, but there is no doubt that the exciting cause is hematogenous, probably some mild irritant substance acting continuously over a long period. The most important causes clinically are gout and the gouty diathesis (uric-acid or lithemic diathesis), and alcohol. Although the latter more often produces a diffuse nephritis, it may be a factor, perhaps an indirect one, in the production of chronic interstitial nephritis. It is possible that the excessive ingestion of alcohol leads to the formation of poisons (alcohologenic toxins) in the intestinal canal, which, when absorbed, may act upon the liver and kidney, causing chronic fibrosis. Syphilis is another factor. There may be other poisons of metabolic origin, in addition to those of the uric-acid group, that may cause chronic interstitial nephritis. Lead poisoning (plumbism, saturnism) may give rise to it, either directly or by first causing arteriosclerosis. The possibility of lead poisoning should be especially kept in mind in seeking the cause of a chronic interstitial nephritis in young persons. In a large number of cases there is a history of mental strain, and it would seem as if this stood in some causative relation to the Bright's disease. How it acts is not easily determined. It may be that, through the medium of increased blood-pressure, it produces primarily an arteriosclerosis, and all causes giving rise to the latter are capable of bringing about renal changes. Senator states that diabetes, especially in early life, may lead to chronic interstitial nephritis. Heredity is a factor of importance; it is often possible to trace the disease through several generations.

A localized form of chronic interstitial nephritis follows the healing of abscesses, wounds, infarcts, or gummas in the kidney, the destroyed tissue being eventually replaced by a scar, which in the case of the healed gumma is usually stellate in shape. A more or less diffuse form, not of hematogenous origin, is that following ascending inflammation of the urinary tract, being secondary to pyelonephritis. Unilateral granular kidney is, according to Fürbringer, always due to nephrolithiasis.

Chronic interstitial nephritis is most common in men of middle life (beyond the age of forty), but it may occur in adolescence, and even in childhood. On account of its insidious character and its long duration (ten to twenty years), it is not always possible to decide when it began; for persons in apparently good health may have the disease.

A constant concomitant of this form of nephritis is hypertrophy of the left ventricle of the heart. Retinal changes and sclerosis of the blood-vessels are also frequently associated with it. These and other disturbances accompanying Bright's disease will be discussed later.

Pathologic Anatomy.—The kidney is small, hard, and granular. It may be reduced to one-third its normal size; indeed, it is at times so small that there may be doubt whether the little body found in the accustomed place is actually the kidney. In advanced cases the weight is from 50 to 70 grams. The kidney is embedded in a large amount of adipose tissue, which is often adherent to the capsule. Not rarely the two organs are unequal in size (asymmetric kidneys; see Fig. 300). The capsule is firmly adherent, and on its removal the cortex is torn. The latter is highly granular, the granules corresponding to parenchyma, the depressions to contracted bands of connective tissue. Cysts are often present on the surface, and are filled with urine or with a yellowish-green colloid material. The large cysts show ridges on their walls, as an evidence of their formation by the confluence of smaller cysts. The color of the kidney is usually reddish, but it varies. The kidney offers considerable resistance to the knife, which may creak on cutting through. The cortex is greatly reduced in width, and at some points may be almost absent, the base of the pyramids reaching to the surface. Its color is mottled, with reddish striæ or dots. The pyramids are absolutely reduced in size, but relatively increased, making up by far the greater part of the cut surface. Bands of fibrous tissue extend into them from the cortex. Calcareous infiltration and deposits of urates are often present. Cysts may be found on the cut surface; they involve the cortex primarily, but may extend part way into the medulla. The fat in the pelvis is greatly increased; the cut arteries stand out prominently, and do not collapse.

Pathologic Histology.—The principal lesions are in the cortex, and consist of an overgrowth of connective tissue and destruction of the glomeruli. The tubules and intertubular tissue, and the blood-vessels also, show changes. The intensity of the lesions varies with the duration of the disease. The distribution is not universal throughout the cortex, but is especially marked in the labyrinth, although not confined to it.

Glomerular Changes.—Many of the glomeruli are destroyed, particularly those nearest the capsule. The capillaries are obliterated, and the entire tuft may be converted into a homogeneous or finely granular hyaline ball, either anuclear or with a few distorted nuclei scattered through the center. In some the degeneration is confined to the periphery, a hyaline band surrounding the remaining nuclei. These hyaline balls are fused with the surrounding tissue, and cannot be shaken out when the unmounted section is agitated. In other cases the glomerulus is surrounded by a thick fibrous capsule, as much as from 60 to 65 μ in width, with concentrically arranged nuclei. The "visceral" epithelium of Bowman's capsule and the glomerulus within may be intact. Often the capsular space is widened, and the glomerulus is abnormally rich in nuclei. A thickened capsule

may also surround hyaline glomeruli. In addition to these degenerated glomeruli, it is not uncommon to find very large highly cellular Malpighian bodies, which are the result of compensatory hypertrophy. The small hyaline balls are about $100\ \mu$ in diameter, while the hypertrophied glomeruli attain a diameter of $275\ \mu$ or more. The glomeruli are closer together in the small contracted kidney than they are normally in adult life.

Tubular Changes.—The tubules representing excretory ducts of the glomeruli undergo atrophy when the latter are destroyed. The atrophied tubules are small and collapsed, their cells shorter and more cubical. The nucleus stains more darkly than normally. At times the cells are detached,



FIG. 311.—Primary chronic interstitial nephritis; small granular kidney: *a*, hypertrophied glomerulus; *b, b, b, b*, hyaline glomeruli; *c*, round-cell infiltration; *d*, dense fibrous tissue; *e*, dilated tubule; *f, f*, compressed tubules.

and lie as a ring or separately in the lumen. Hyaline and slightly greenish-colored (waxy or colloid) tube-casts are present. Some of the tubules are dilated into large or even cystic spaces. Such dilated tubules are often found in groups in the medullary rays of the cortex. The epithelium is very low, the striated border is lost, and the nucleus is almost at the free border of the cell. Some tubules are apparently hypertrophied, and as their cells are large and well formed, the hypertrophy is evidently a compensatory process, such as we have seen in the case of the glomeruli. Sometimes there is a pronounced multiplication of tubules, with complicated foldings, that is suggestive of an adenomatous growth.

Interstitial Changes.—There is a marked increase of the stroma, both in

the cortex and in the pyramids, between the tubules, about the glomeruli, and about the blood-vessels. All stages of connective-tissue proliferation may be seen, from the cellular to the homogeneous, scar-like fibrous tissue. The overgrowth is especially marked about the glomeruli and between the cortical tubules. In the pyramids the newly formed fibrous tissue is often quite cellular. At times, if an acute process is superadded, there is an intense infiltration of round cells, some of which have the appearance of plasma-cells. Calcification of the newly formed fibrous tissue is quite common. The blood-vessels are thickened—not to the same extent, perhaps, as in the so-called arteriosclerotic kidney, but often to a great degree. The process is an endarteritis, and affects especially the smaller intertubular vessels, the lumen of which may be greatly reduced through a thickening of the intima. On measuring one of the small, thick vessels, the writer found its whole diameter to be $49\ \mu$, of which the lumen was represented by only $11\ \mu$. When the larger arteries are involved the media is also greatly hypertrophied.

(c) *Arteriosclerotic Nephritis*.—Histologically and anatomically the difference between this and the preceding is not great. In the pure form of arteriosclerotic kidney there is a primary arteriosclerosis without any noteworthy changes in the general stroma; pure forms are, however, rare, and inflammation of the interstitial tissue combined with sclerosis of the blood-vessels is often found. Obviously, it is difficult to separate this form from the chronic interstitial nephritis described above, as the inflammation in the latter, although primarily affecting the general stroma, may and frequently does cause disease of the blood-vessels.

Arteriosclerosis in the kidney, as well as elsewhere, is frequent in old age, and the so-called *senile nephritis* is really an arteriosclerotic nephritis. The latter is therefore chiefly found in advanced life. It may occur earlier, and then is due to the special causes of arteriosclerosis, as already given.

Pathologic Anatomy.—The kidney is normal in size or smaller, rarely larger; hard and irregularly granular. The color is cyanotic or reddish. The capsule strips easily, but sometimes is adherent in places. On section the cortex is reduced in size and of a dark-red color; the pyramids are also dark and congested. The arteries project and gape like small stiff tubes.

Pathologic Histology.—The prominent feature is a great thickening of the blood-vessels, which is not, however, uniform in all parts of the kidney, being generally focal in distribution. The intima is especially thickened (arteriocapillary fibrosis of Gull and Sutton). If the arterial disease is advanced, the glomeruli fed by the affected vessels undergo retrograde changes—hyaline degeneration, obliteration of the capillaries, and slight thickening of the capsule. There is very little increase of the general fibrous tissue in the pure arteriosclerotic kidney; but, as already intimated, it is not uncommon to find the intertubular stroma the seat of round-cell infiltration or of proliferative processes.

Amyloid Kidney.—The causes and microscopic features of this have been described. The amyloid degeneration may occur alone, but more often is associated with one of the various forms of nephritis. It is possible to distinguish three types of the amyloid kidney:

(a) *Pure Amyloid Degeneration*.—In this there is an amyloid degeneration of the blood-vessels, including the glomerular capillaries, with preservation

of the parenchyma. To the naked eye the kidney may present a normal appearance.

(b) *The Amyloid Large White Kidney*.—In this the features of chronic diffuse nephritis without induration (chronic parenchymatous nephritis) and amyloid degeneration are combined. This is the most frequent form, and produces marked enlargement of the kidney.

(c) *Amyloid Contracted Kidney*.—This presents the characteristics of chronic interstitial nephritis with amyloid degeneration.

The Urine in the Different Forms of Nephritis.—In the different forms of Bright's disease the urine undergoes marked changes in both its chemical and its physical characters. Taken in their totality, these changes are more or less characteristic in each of the forms; but there is no

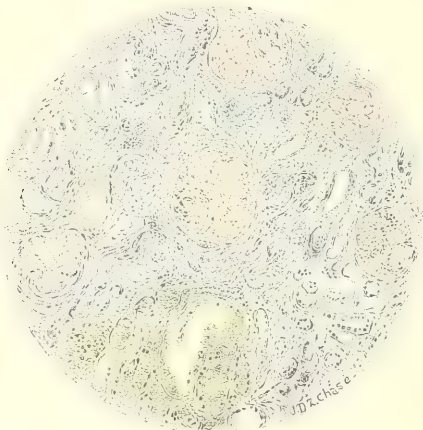


FIG. 312.—Chronic diffuse hemorrhagic nephritis with amyloid degeneration. Ocular 1 in.; obj. $\frac{3}{8}$.

single feature of the urine that can be considered as peculiar to any one of the varieties of nephritis.

Acute Diffuse Nephritis.—The quantity of urine is greatly diminished (oliguria); there may even be complete suppression (anuria). The specific gravity varies inversely with the quantity, although in rare cases it is low when the quantity is small. Blood is often present, and gives to the urine a dark-red or smoky color. The sediment is abundant, and contains tube-casts, red corpuscles, leukocytes, and detached epithelial cells. The tube-casts are hyaline, leukocyte, blood, or epithelial casts. A large amount of albumin is present (0.2 to 1 per cent.). The urea is diminished; the xanthin bases are increased; the reaction of the urine is acid.

Acute Interstitial (Nonsuppurative) Nephritis.—The urine may be entirely normal; generally a moderate amount of albumin is present; the sediment contains leukocytes and tube-casts.

Chronic Diffuse Nephritis without Induration.—In the large white kidney the urine is diminished in quantity, the specific gravity increased,

and the reaction acid. Large amounts of albumin are present (from 0.2 to 5 per cent.). The urea is diminished in quantity, as are also the chlorids and phosphates. The sediment contains hyaline, granular, and fatty casts, leukocytes, and epithelial cells. In the hemorrhagic form of chronic nephritis blood and blood-casts are present.

Chronic Diffuse Nephritis with Contraction (*Secondary Contracted Kidney*).—The quantity is normal or increased; the specific gravity normal or lessened. Albumin is present in abundance. The sediment contains red blood-corpuscles, hyaline casts, and fatty epithelial cells.

Primary Chronic Interstitial Nephritis (*Granular Kidney*).—The quantity of urine is greatly increased (from 7 to 10 pints a day). The color is very pale. The specific gravity is low (1007–1012); even when the quantity is reduced the specific gravity is not notably increased. Albumin is present in small quantities (up to 0.25 per cent.), but may be absent, especially in the morning urine. The urea is reduced in quantity, as are also the other solids. There is very little sediment; by the use of the centrifuge, however, a few hyaline casts and leukocytes may be demonstrated.

Amyloid Kidney.—The features of the urine in amyloid degeneration have already been described.

Functional and Organic Disturbances resulting from Nephritis.—Disease of the kidneys has a marked effect upon the general organism. The cause of this effect is to be found in an alteration of the blood, produced primarily by the retention of waste products of metabolism; also probably to some extent by the failure of elimination of accidental substances, soluble or insoluble (bacteria), which the normal kidney is able to excrete; moreover, it is possible that the kidney has an internal secretion, which, in inflammation of the organ, is either diminished or modified.

The Urine.—The specific effects of the various types of nephritis on the urine have already been discussed. Considering the subject now from a general standpoint, we find that the urine made by diseased kidneys is poor in solids, particularly in nitrogen compounds. This diminution is not always demonstrable in urine coming from the bladder, either because only one kidney is diseased, the other compensating for the deficiency; or because the renal affection is focal in character, and the healthy portions become more active in proportion to the incapacity of the diseased areas. While the diminution in solids can be estimated to some extent by quantitative chemical analysis, it is far more easily and certainly demonstrated by a physical method, which consists in the determination of the freezing-point of the urine—the method known as *cryoscopy*. This was introduced into medicine by Korányi,¹ and by Caspar and Richter.² The freezing-point of any liquid is governed by the number of molecules contained in solution; the quality of the molecules is not of consequence, except that those of very large size—albumins and other colloids—do not influence the freezing-point to any extent. The freezing-point, therefore, is an index of the molecular concentration of a liquid, and also of the osmotic pressure or tension, since this is always proportionate to the molecular concentration. Normal urine has a freezing-point from 1.3° to 2.3° C. below that of distilled water. Nephritis and other morbid states of the kidney cause

¹ *Zeit. f. klin. Med.*, xxxiii., 1, and xxxiv., 1.

² *Funktionelle Nierendiagnostik*, Berlin and Vienna, 1901.

this depression of the freezing-point below that of distilled water (expressed by the symbol Δ) to be lessened, indicating that there is a diminution of solids, or *hyposthenuria*. In nephritis, Δ usually equals 1° C. or less; that is, the freezing-point approaches more nearly that of water.

The ratio of Δ to the percentage of sodium chlorid in the twenty-four hours' urine varies normally from 1.23 to 1.69. In nephritis the ratio is extremely variable, and it is possible to distinguish two types—one in which $\frac{\Delta}{\text{NaCl}}$ is greater, and one in which it is much less than normal. Clinically no difference in the two types is recognizable; whether they differ anatomically has not been determined.

Disease of the kidney also affects the functional power of the organ with respect to certain extraneous substances, in the elimination of which the normal kidney shows a constant behavior. Normally, when *methylene-blue* is injected or introduced by the mouth it rapidly appears in the urine. After a hypodermic injection of 0.05 gram the elimination, shown by a greenish color of the urine, begins in fifteen minutes, reaches its maximum in three hours, and continues for forty-eight hours. If 0.1 gram is given by the mouth the substance appears in the urine in from fifteen to twenty-five minutes, and continues to be eliminated for from three and a half to four days. Now, it has been found that in chronic interstitial nephritis the elimination is retarded, while in chronic parenchymatous nephritis (large white kidney) it is usually accelerated; that is to say, the *permeability* of the organ to methylene-blue is decreased in the former and increased in the latter. Hence methylene-blue may be used as a diagnostic test of the state of the kidney; but there is a possible fallacy, in that the dye may be eliminated in part as a colorless substance (leukomethylene-blue).

Phloridzin Diabetes.—The injection of 0.005 gram of phloridzin produces a glycosuria which, according to the majority of authors, is of renal origin. The glycosuria begins in half an hour after the injection, and lasts for from two to four hours, the quantity of sugar eliminated varying from 1 to 2 grams. In cases of nephritis and other renal disorders the appearance of the glycosuria is delayed and the quantity of sugar is less than that secreted by normal kidneys.

Hippuric Acid Formation.—The kidney has the power to combine glycocholic acid, a product of proteid metabolism probably made in the liver, with benzoic acid, to form hippuric acid. Normally, this acid is found in the urine only in traces, but it can be greatly increased by the administration of benzoic acid. In renal disease the power of uniting this acid with the glycocholic acid of the blood is diminished or abolished.

The Blood.—There is anemia in all forms of nephritis. It is most noticeable in chronic diffuse nephritis (chronic parenchymatous nephritis), but also reaches a high degree in granular kidney. The reduction affects the red corpuscles and, to a yet greater extent, the hemoglobin. The leukocytes, according to Cabot,¹ are not increased, except in hemorrhagic nephritis and in uremia. Associated with the anemia is a hydremia, which is especially marked in chronic parenchymatous nephritis. The specific gravity of the blood and of the serum is reduced. That of the latter, normally 1030, may sink to 1020, or even to 1015. The red corpuscles also contain more water than normally. The cause of the hydremia is not definitely known. Accord-

¹ *Clinical Examination of the Blood*, New York, 1898.

ing to Krehl,¹ it is due to retention of water, owing to inactivity of the skin and insufficient elimination of water by the kidneys. Another factor is the loss of albumin in the urine, and there are probably additional causes that are yet to be discovered. In rare cases there is no hydremia.

The blood in nephritis is richer in urea, the normal being from 0.01 to 0.05 per cent. The quantity of sodium chlorid is not changed in any constant way; it may be augmented or lessened. The other urinary constituents, in so far as they are not made in the kidneys themselves, are increased in the blood. This accumulation of waste products produces a rise in the molecular concentration of the blood, which in turn manifests itself in a depression of the freezing-point. Normally the freezing-point of blood is from 0.56° to 0.58° C. below that of water; in nephritis the freezing-point (λ or δ) is at a lower level. Richter and Roth² have shown that after the experimental production of nephritis in animals the molecular concentration of the blood is directly proportionate to the extent of injury to the kidney. It was at first thought that the retained molecules were chiefly sodium chlorid, but it has been proved that the molecules are true metabolic products. A fact which somewhat lessens the value of molecular concentration as an index of retention in nephritis has been pointed out by Korányi.³ He has shown that the diet, which normally has but little effect upon molecular concentration, is of decided influence when the kidneys are diseased. The concentration is raised by nitrogenous foods, and lowered by carbohydrates.

Toxemia.—According to the investigations of Hughes and Carter,⁴ the blood in nephritis, and especially in uremic states, contains, in addition to the urinary waste products, a poison destroyable by heat and dialyzable with difficulty. This poison is capable of producing in dogs renal changes, and even uremia. Of its nature, apart from the probability that it is an albuminous body, nothing is known. Reference will again be made to it under Uremia.

Viscosity.—According to recent investigation, there is an increase in the viscosity of the blood in nephritis. If this is true, we may find in this viscosity one of the factors causing the increased blood-pressure and the cardiac hypertrophy common in chronic renal disease.

Uremia.—Uremia is a symptom complex produced by the action of poisons that have accumulated in the blood by reason of insufficient activity on the part of the kidneys. It may occur in the course of any one of the forms of nephritis described. Nearly all functions are disturbed, but particularly those of the nervous, digestive, and respiratory systems.

Etiology.—The exact cause of uremia is still in doubt. Traube attributed the condition to edema and anemia of the brain. The former, he thought, was due to hydremia and increased pressure in the arterial system, while the anemia was conditioned upon the pressure produced on the arteries by the exuded serum. This theory, however, is not tenable. Uremia may occur when there is no edema elsewhere in the body, in which case there is no reason to suppose that there is edema of the brain; furthermore, the experimental injection of enormous quantities of fluid into the circulation, thus raising the blood-pressure, does not bring about edema.

¹ *Pathologische Physiologie*, 1898, 180, Leipsic.

² *Berlin. klin. Woch.*, 1899, 657 and 683.

⁴ *Am. Jour. Med. Sci.*, cviii., 177 and 268, 1894.

³ *Ibid.*, 97.

A more plausible theory is that which ascribes uremia to the retention of urinary waste products. Nearly every one of the constituents of the urine has in turn been looked upon as the responsible agent. The first to be so considered was naturally urea; but experimentally this substance is not capable of producing uremia, and uremia may occur in cases in which the elimination of urea is normal. Frerichs then advanced the hypothesis that ammonium carbonate, a decomposition-product of urea, was the cause of uremia; but it was soon conclusively demonstrated that uremic blood is free from ammonium carbonate.

One by one, the urinary constituents were tested, and none was shown capable of producing the symptoms of uremia. The only one possessing active toxic properties was found to be the potassium salts, especially potassium chlorid. But while potassium is decidedly toxic, and is capable of producing dyspnea and convulsions, its injection does not reproduce the clinical picture of uremia.

Search was then made for organic substances in the urine, and Bocci found an alkaloidal body which he acclaimed the cause of uremia. Then appeared the work of Bouchard, who isolated from the urine various toxic principles—altogether seven—to which he ascribed uremia. These toxic substances are absent from uremic urine because they are retained in the system. The existence of Bouchard's "urotoxins" in the urine has been repeatedly denied, and the theories based upon their supposed presence have been combated. Posner and Vertun have shown that the toxic effect of urine when injected is in a large measure due to difference in molecular concentration. Contamination by bacteria is also capable of causing the presence of poisonous substances in the urine.

Von Jaksch and von Limbeck found a lessening of the alkalinity of the blood during uremia, and thought that this was the cause of the condition. The diminution of alkalinity was supposed to be due to an increase in the lactic acid in the blood, but this could not be confirmed by Gottheiner¹ and others. Landois,² from a series of painstaking experiments, concluded that uremia was due to the action of urinary extractives and salts upon the brain.

Willgerodt³ produced uremia by conducting the ureters into the peritoneal cavity, so that the urine flowed directly into this cavity, and concluded that the kidneys themselves make the substance to which uremia is due.

An important research was made by Hughes and Carter,⁴ who found in the blood-serum in uremia a body capable of producing uremia and nephritis in dogs. This body, which they were not able to isolate, was not readily dialyzable, and was rendered innocuous by heat. This indicates that it is of the nature of a proteid or an enzyme. The investigation was not carried far enough to place the theory on a firm footing.

Ajello and Parascandolo⁵ enunciated the view, based upon insufficient experimentation, that uremia was due to the absence of an internal secretion furnished by the kidney. It is not impossible that a loss or perversion of an internal secretion is a factor in the production of uremia, but there is as yet no reliable evidence.

From this brief review of the subject, it is apparent that the cause of

¹ *Zeit. f. klin. Med.*, 1897, xxiii., 315.

² *Mittheil. aus den Grenzgeb. der Med. u. Chir.*, 1897, ii., 461.

³ *Lo Sperimentale*, 1895, xlix.

⁴ *Die Uraemie*, 1891.

⁵ *Loc. cit.*

uremia is still unknown, and that we can assert nothing more than that uremia is an auto-intoxication with retention products.

Pathologic Anatomy.—In addition to the usual lesions of nephritis and the cardiovascular consequences commonly found, uremia, whether spontaneously or experimentally induced, gives rise to structural alterations in various organs. In the nervous system there are found edema, hyperemia, and small hemorrhages in the membranes, together with similar changes in the substance of the brain and cord. The ganglion-cells, with Nissl's stain, present vacuolation and chromatolysis, while Golgi's method reveals—not present constantly, however—varicose atrophy of the dendrites and shrinking of the processes of the neuroglia-cells. These ganglionic changes are very widespread throughout the cerebrospinal axis, and probably occur also in the spinal ganglia. There is sometimes round-cell infiltration about the small blood-vessels in the brain and cord. These various lesions do not, however, adequately explain all of the nervous symptoms of uremia, particularly not the focal symptoms, such as uremic hemiplegia. The parenchyma of other organs also presents degenerative changes. Korowin¹ found cloudy swelling in the myocardium, with enlargement of the muscle-nuclei, hyaline degeneration of the vessel-walls, and foci of round-cell infiltration. The cardiac ganglia were the seat of degenerative changes. In the spleen cloudy swelling and vacuolar degeneration of the endothelium were found. The stomach and intestines presented acute catarrhal inflammation, with degeneration of the surface epithelium and inflammatory round-cell infiltration. The liver-cells were the seat of advanced granular degeneration and vacuolation. In the pancreas and the salivary glands signs of exaggerated secretory activity, shown by increase in size and number of the granules, were found in the early stages; in later stages the cells also suffered degenerative changes. The endothelium of the blood-vessels throughout the body was altered, and there were small hemorrhages and pigmentary deposits in the vessel-walls.

A common autopsy lesion in uremia is edema of the lungs. Pneumonia is also not rare. Ulceration of the large intestine, resembling that produced by dysentery, sometimes occurs. Changes in the retina are quite common. They are, according to Khokhriakoff,² in addition to transient edema, varicose thickening of the nerve-fibers, vacuolar degeneration of the ganglion-cells, with enlargement of the pericellular spaces, displacement of the nucleus in the cells of the external granular layer, the formation of clear spaces by reason of edema in the granular and reticular layers, swelling of the endothelium of the vessels and widening of the perivascular spaces, and thickening of the fibers of Müller.

Cardiovascular System.—*Pathologic Physiology.*—Irregularity of the heart, gallop-rhythm, and intermittency are common, especially in chronic forms of nephritis. The arterial tension is usually increased, to the greatest degree in contracted kidney.

Pathologic Anatomy.—Hypertrophy and often dilatation of the heart are usually found in the chronic forms of nephritis, particularly the granular kidney. The left ventricle is principally affected, not rarely also the right. In amyloid disease cardiac hypertrophy is generally absent, on account of the depression of the general health. The cause of cardiac hypertrophy is

¹ *Die pathologische Anatomie der Uraemie*, Inaug. Diss., St. Petersburg, 1897.

² *Gaz. de Botkine*, 13, 1897.

increased pressure in the arterial system, but it is possible that in addition to this there is a direct stimulation of the heart, leading to hypertrophy. The cause of the increased arterial pressure has been a matter of controversy for many years. Some, particularly Traube, have attributed it to mechanical causes—to a reduction of the vascular territory in the kidney; others, to contraction of the vessels, produced by the stimulation of the vasomotor system by an irritant in the blood, this irritant being the retained poisons. The latter, the chemical theory, which was foreshadowed by Bright, is the one now generally held. The possible influence of increased viscosity of the blood has been mentioned.

Arteriosclerosis is common in nephritis, but it is difficult to place it in proper relation with the disease. In the first place, it may be due to the kidney disease, being a consequence of the irritant action of the retained poisons; secondly, it may have preceded the nephritis; and thirdly, it and the renal inflammation may be co-ordinate and due to the same cause.

Pericarditis and Endocarditis.—The development of these are favored by renal disease. In the majority of cases the serous-membrane inflammation is due to infection, to which kidney disease predisposes; but there appears to be a so-called uremic pericarditis of nonmicrobic nature. The acute pericarditis of nephritis is usually fibrinous in character.

Edema.—Edema is a common feature in nephritis, especially in acute glomerulonephritis and in chronic diffuse nephritis; it is rare in the chronic interstitial form. In acute glomerulonephritis it appears very early, and reaches enormous degrees. Beginning in the lower eyelids, in the fingertips, or in the ankles, it soon becomes general, the affected parts being pale and soft. The edema has a tendency to involve also the serous cavities, the lungs, and the mucous membranes.

The origin of the edema is variously explained; but it is unnecessary to enter into a discussion of all the theories that have been advanced. The one now generally adopted is that of Senator, who attributes the edema to the action of certain poisons circulating in the blood and acting on the blood-vessels. They first act on the capillaries of the glomeruli, and then, if in sufficient strength, or if acting sufficiently long, on the blood-vessels of the skin, serous membranes, etc. Lazarus-Barlow¹ also attributes the edema to the accumulation of waste products in the blood and tissues. In his opinion, this accumulation indirectly leads to an increased flow of lymph, which cannot all be carried off by the natural channels, the excess remaining as edema. The edema fluid in the serous cavities in Bright's disease contains the lowest quantity of albumin met with in transudates (from 0.1 to 0.8 per cent.).

In chronic interstitial nephritis edema sometimes comes on toward the end, and is then in a large measure due to cardiac failure.

Digestive Tract.—Some of the organic changes produced in the digestive tract by Bright's disease have already been considered under the heading of Uremia. Among the functional disturbances we find salivation, loss of appetite, and vomiting. Peristalsis is increased by the retained waste products, especially by urea, which, when excreted into the intestinal tract, is converted into ammonium carbonate, an irritant stimulating peristalsis. According to Lukjanow,² however, this irritation is not alone

¹ *Manual of General Pathology*, 834, Philadelphia, 1898.

² *Pathologie der Verdauung*, 256, Leipsic, 1899.

sufficient to explain the diarrhea, for which organic changes, such as edema and inflammation, are also partly responsible. Duodenal ulceration and ulceration of the colon are additional structural changes that may accompany nephritis.

Respiratory Tract.—Dyspnea (renal asthma) and Cheyne-Stokes' breathing occur in uremic conditions. At times there is a large amount of ammonium carbonate in the breath, demonstrable by holding in front of the mouth a glass rod which has been dipped in hydrochloric acid. Regarding the source of this, the prevailing opinion now is that it comes from the decomposition of urea and proteid substances in the mouth, and that it is no evidence of the presence of ammonium carbonate in the blood. Among anatomic changes, bronchitis, pneumonia, pleurisy, edema of the glottis, hydrothorax, and edema of the lungs must be mentioned. Clinically, the coexistence of nephritis makes the prognosis in pneumonia more grave.



FIG. 313.—Miliary tuberculosis of the kidney (Reynolds).

Nervous System.—Headache, neuralgia, convulsions, coma, hemiplegia, aphasia, delirium, and other mental disturbances are phenomena of the uremic state. The organic changes have been given in detail under Uremia.

Skin.—Skin lesions are not common in nephritis: pruritus, eczema, and other eruptions, and gangrene, have been described. In uremia there is usually suppression of the sweat secretion.

Fever.—Fever occurs in acute Bright's disease, and sometimes in uremia. In the latter it may be very high, although, as a rule, the temperature is subnormal, particularly in experimental uremia. The cause of uremic fever is not definitely known. It may be due to accidental infective complications, or to the pyretogenic action of retained waste products.

Tuberculosis.—Tuberculosis is frequent in the kidney. The infection

is usually hematogenic, but it may be brought about by upward extension along the urinary tract, or by extension from neighboring organs, as the suprarenal glands. It is more common in the male sex; in childhood this preponderance of the male is very noticeable. Hamill, in 46 cases in which the sex was given, found 32 in boys, and 14 in girls. Facklam (quoted by Hamill), in 103 cases of all ages, chiefly adults, found 30 in the male, and 73 in the female sex. The disease presents itself in two forms—as miliary tuberculosis and as chronic or caseous tuberculosis.

The first is far more common, and is nearly always secondary, being met with in general miliary tuberculosis; but even in cases of extensive chronic tuberculous disease of the lungs, without general tuberculosis, a few miliary nodules may be observed in the kidneys, often only in one of them. It is possible that there may be a miliary tuberculosis of the kidney that to all intents and purposes is primary. A small lesion probably exists elsewhere, but there is no general miliary tuberculosis nor advanced pulmonary phthisis.

The bacilli brought by the renal arteries are deposited in the glomeruli, but may under certain conditions also find their way into the uriniferous tubules, giving rise to the so-called *elimination tuberculosis* (Cohnheim, Meyer).

The tubercles appear as grayish-white nodules, varying in size, sometimes very numerous, at others in small numbers, and are usually surrounded by capillary injection. They are most abundant in the cortex, rarer in the pyramids. Occasionally, by coalescence, larger nodules are produced, which may present a caseous center.

Microscopically the tubercles are in some cases of the typical form, and rather sharply demarcated; at others they appear more diffuse, with a partly degenerated center. The tubules in the immediate neighborhood show cloudy swelling.

Chronic tuberculosis is the characteristic form of renal tuberculosis. Of the greatest interest is the question whether this form may occur primarily in the kidney.

In considering this question, it may be said that tuberculosis of the urogenital tract may be like that of the respiratory tract, primary, although it is never safe to assume this unless careful search has been made in all possible places, as, *e. g.*, in the tonsils and in the bronchial and other lymph-glands, for tuberculous disease.

Now, in the urogenital tract we find that tuberculosis of the kidney is often associated with tuberculous inflammation of other parts of this tract—as the pelvis, ureter, bladder, epididymis, testicle, seminal vesicle; and many writers have held that, whether the tuberculosis of the tract be primary or secondary, the involvement of the kidney is nearly always secondary to disease of lower parts. Such at least was the view of Rokitansky, with whom Klebs, Simon, and others agree. Guyon and Albarran also believe that the disease generally ascends. Strong grounds exist, however, in favor of the contrary opinion, viz., that the disease is more frequently descending than ascending, and Israel,¹ Steinthal, Camargo, and Hamill defend this theory. Hamill found that in 55 cases of renal tuberculosis in children collected by him nearly all began in the kidney. Israel believes primary renal tuberculosis to be very common. Among 21 cases operated upon by

¹ *Deutsch. med. Woch.*, July 14, 1898.

him, 16 were apparently instances of primary infection. One-third of all cases of pyogenic processes in the kidney are, in his opinion, tuberculous; in one-fourth tuberculosis is primary in the kidney.

This does not, we think, hold good to the same extent in adults; but even in them the kidney is more often the starting point of urogenital tuberculosis than the organs situated farther down. Judging from the statistics of surgeons, the disease is most often unilateral, while the autopsy records show it to be more frequently bilateral. Disease in one kidney may lead to infection of the other through the circulation or through infection ascending from the bladder along the ureter to the unaffected kidney. At times one kidney is almost completely destroyed, while the other, macroscopically at least, is absolutely free from tuberculosis. Statistics show that the disease occurs almost as frequently in the right as in the left kidney.

Three anatomic forms can be distinguished: (a) The caseous form with cavity formation, which is the most frequent (81 per cent. of Israel's cases). It usually begins in one pole of the kidney, generally the lower, in the form of a small grayish nodule, which enlarges and becomes caseous. Extending by continuity, the process involves adjacent parts until perhaps the entire kidney is affected. The caseous areas break down and leave cavities, which are separated one from the other by bridges or septa of renal tissue, which on section are also extensively tuberculous.

Pathologic Anatomy.—The kidney is usually enlarged, but the general outline is preserved; in rare cases, although the tuberculosis is most extensive, there is no enlargement, even a reduction in size; some of these are probably instances of tuberculosis attacking a contracted and fibroid kidney. The freedom with which urine and discharges can escape along the ureter also influences the size of the organ. At times there is very little in the appearance of the uncut kidney to indicate the existence of tuberculosis. Usually the organ gives a sensation of fluctuation or has a doughy or mushy feel, and shows division into larger lobes or is bossellated. The elevations, large or small, represent tuberculous cavities, and about them the capsule is usually much thickened, and is not easily stripped. There may also be dense adhesion between the capsule and the paranephric fatty tissue. On section the kidney appears sacculated, and in advanced cases it consists of an agglomeration of irregular cavities extending from the pelvis to the cortex, and filled with a yellowish-white creamy or curd-like material, the latter probably resulting from the absorption of fluid. At the base of each cavity or cheesy area there may be a rim of cortical tissue, and often it appears as if the process had been arrested just at the boundary line of cortex and medulla. In very old cases there may be no renal structure visible. When the broken-down material is washed out, the walls are either clean or a layer of curd-like material forms the lining of the cavities.

The variety of renal tuberculosis described is often associated with inflammation of the perinephric and paranephric tissues. The fatty capsule may be greatly thickened and fibrous and completely fused with the capsula propria of the kidney. Perinephric and paranephric abscesses may also occur, and was noted in 5 of the 55 cases collected by Hamill. The abscess may or may not be tuberculous. Israel also describes a condition in which a spongy granulation-tissue, tuberculous in nature, extends between the kidney and the thickened capsule; in rare instances isolated caseous nodules are present in the fatty capsule. The process may extend to the

renal vein, as in a case of Hanau,¹ in which the caseous material in the vein was the starting point of a general miliary tuberculosis. The urine usually contains larger quantities of pus, and is acid in reaction unless there is cystitis. Blood may be present, and at times appears very early from extension of the disease to the renal vessels (Trantenroth²). Tubercle bacilli are found, and occasionally appear in groups suggesting a pure culture.

(b) The second form of renal tuberculosis is tuberculous ulceration of the apices of the papillæ, which is clinically characterized by early and profuse hematuria.

(c) The third form is a nodular tuberculosis, in which the entire organ is studded with whitish nodules, pinhead-sized to pea-sized, which exhibit no tendency to caseation and softening. The surface of the kidney after

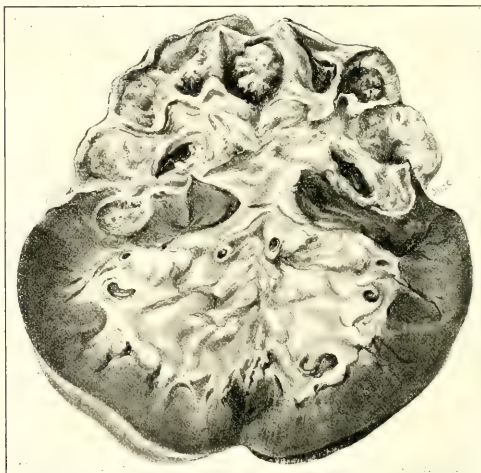


FIG. 314.—Tuberculosis of the kidney limited to the upper pole.

removal of the capsule is marked by rounded elevations, the tubercle nodules, and on section the distribution of the nodules is distinctly radiating, resembling the surface of section of surgical kidney.

The pelvis is often involved in tuberculosis of the kidney; at first miliary tubercles appear, but they soon enlarge, coalesce, and then break down, leading to the formation of ulcers. Frequently the process extends to the ureter also, and finally down into the bladder. Not rarely neighboring lymph-glands are infected; the perinephric tissues, as already stated, may become involved and a perinephric abscess may form.

Syphilis.—Syphilis of the kidney is rare, if we confine the term syphilis to the characteristic lesion, the gumma. Gummas do, however, occur, both in acquired and in congenital syphilis, and are found in the

¹ *Virchow's Archiv*, cviii., 22, 1887.

² *Mittheil. aus den Grenzgebieten der Med. und Chirurgie*, i., 1895.

cortex or in the pyramids; rarely in both at the same time. They vary in size from that of a pinhead to that of a hazelnut, and are surrounded by a grayish or hyperemic zone. As many as from 20 to 60 may be found. Occasionally suppuration takes place. Sometimes there is a diffuse gummatous infiltration, causing marked enlargement of the kidney, as in a case observed by Bowlby,¹ in which the kidney weighed 17 ounces and looked like a huge syphilitic testicle. The histologic features of gummas in the kidney are identical with those of gummas in other organs, and have been detailed under Syphilis. The healing of gummas is accompanied by the formation of scars, which are usually superficial and somewhat stellate in shape. When large and multiple they may give the organ a lobulated appearance; not rarely one kidney is more markedly affected than the other. The scars are seen more often than the gummas, and must be distinguished from embolic cicatrices. As the latter result from the healing of infarcts, search may reveal the presence of fresh infarction and also the existence of a source of emboli. In the case of syphilis, evidences of the disease are usually found elsewhere in the body; the history, if obtainable, is also of value. In very rare instances the kidney is the seat of miliary gummas (miliary syphilomas), a condition comparable to miliary tuberculosis.

In syphilitic fetuses Hecker found a round-cell infiltration about the smallest cortical vessels, which he considers a characteristic feature of congenital syphilis. There are also, but not constantly, an accumulation of leukocytes in the capsular space and a proliferation of the capsular epithelium. A form of parenchymatous and interstitial nephritis occurring in congenital syphilis has been described by Marchiafava and by Stroebe.

Syphilis may also produce changes in the kidney that are not specific and cannot be microscopically distinguished from those observed in connection with other infectious diseases. According to Fournier, such changes may occur as early as two months after the infection, and present themselves as acute or subacute nephritis. The urine is diminished and contains a large quantity of albumin. Delamare² in one case found only globulin in the urine. According to Renon,³ the kidneys of syphilitic patients are more liable to nephritis than those of other persons (so-called fragility of the kidney).

Leprosy.—Leprous lesions in the kidney are rare. Babes⁴ refers to an observation made by Hedenius of the occurrence of a leprous nodule in the kidney of a leper. Nonspecific inflammations, such as chronic parenchymatous and interstitial nephritis, and even amyloid degeneration, are not rare in leprosy. Babes has often found the *lepra bacillus* in apparently healthy kidneys, especially in the endothelial cells of the glomerular blood-vessels; but the bacilli, it seems, do not penetrate into the capsular space, as they have never been found in the urine.

Glanders.—Glander-nodules are not rare in the kidneys of horses; in human glanders the kidney is seldom affected.

Actinomycosis.—The kidney may be secondarily involved, the point of entrance of the organism usually being the digestive tract—the mouth, the pharynx, or the intestine. In one instance Israel found what appeared to be a primary renal actinomycosis.

¹ *Trans. Path. Soc. London*, 1897.

² *Gaz. des. Hôp.*, 553, 1900.

³ *Presse méd.*, No. 30, 1899.

⁴ *Untersuchungen über den Leprabacillus*, Berlin, 80, 1898.

Leukemia.—The infiltration of lymphocytes occurring in the kidney in leukemia has already been mentioned; allusion is again made to the subject because it seems not improbable that leukemia is an infectious disease. The leukemic lesions differ, however, from the ordinary granulomas in that the cells composing them have no tendency to form connective tissue; nor are they subject in the same degree to degeneration or caseation. Leukemic infiltration may be diffuse or localized.

Lymphomatous nodules are also found in typhoid fever, and sometimes in other infectious diseases.

Tumors of the Kidney.—Benign tumors of the kidney are comparatively rare and usually small; malignant tumors are not infrequent, and possess peculiarities that for a long time made them—and even now make them—pathologic enigmas.

Fibroma.—Fibromas ordinarily present themselves as small, pinhead to



FIG. 315.—Multiple fibromas of the kidney.

pea-sized, grayish-white growths, usually situated in the cortex or just beneath the capsule, but also in the medulla. They may be mistaken for tubercles, but are harder, more glistening, and more sharply circumscribed. In a strict sense they are probably not tumors at all, but products of interstitial inflammation. Clinically, they possess no importance. Histologically, they consist of dense fibrous tissue with mucoid degeneration. Not rarely, long spindle-cells are present, which to all intents and purposes are non-striated muscle-fibers. In rare cases fibromas attain a very large size; thus, Wilkes¹ observed one which weighed 37½ pounds. Sometimes the kidney consists of a conglomerate of fibromas of considerable size, as in the accompanying illustration. In this case some of the tumors were as large as walnuts, and were distinctly encapsulated. Fibromas of large size—up to 10 kg.—not rarely spring from the capsule, and are often mixed with an abundance of unstriated muscle-cells, resembling both macroscopically and microscopically uterine fibroids; and, like uterine fibromyomas, they tend

¹ *Trans. Path. Soc. London*, xx., 224.

to degenerate and to become cystic. In the cyst-fluid cholesterol is often present. Calcification of the solid portions of the tumor is not rare.

Fibromyomas containing striped as well as nonstriped muscle-cells also occur. Busse observed such a case in a woman of fifty-seven years; all stages of transition between striped and nonstriped muscle could be traced.

Lipoma.—Lipomas are occasionally found beneath the capsule of the kidney; they are small and generally multiple. Grawitz believes that these lipomas are congenital, and represent aberrant portions of suprarenal gland tissue (*strumæ lipomatodes aberratæ renis*). Lipomas sometimes reach a large size, as in an instance observed by Warthin, in which the tumor weighed 2 pounds, and microscopically presented the features of a fibrolipoma.

Liomyoma.—This is a tumor composed of unstriped muscle-tissue, and is extremely rare in the kidney; but it occurs, as has been mentioned, in association with fibroma. That such a tumor should arise in the kidney ought not to be surprising; unstriped muscle is found, not alone in the blood-vessels, but also in the capsule and at the points of attachment of the calices. A *liomyolipoma* has also been described; it is supposed to develop from parts of the fibrofatty capsule included between the primitive vesiculi.

Osteoma and **chondroma** have been found in the kidney, but are extremely rare.

Pure myxomas are very rare, but myxomatous degeneration of other connective-tissue tumors is common, and may give rise to the belief that the tumor is really a myxoma.

Cavernous Angioma.—Cavernous angiomas, such as are found in the liver, are also met with in the kidney. They are bright-red masses, from the size of a cherry to that of a walnut, and are usually situated beneath the capsule, sometimes in the pelvis, constituting a cause of hematuria.

Sarcoma.—Sarcoma is the most common renal tumor, and has a very striking tendency to occur in childhood rather than in adult life. It may be congenital; it has been found in stillborn infants. Senator, in a collection of 58 cases, found 38 to occur under the age of ten years, 7 in the first year of life. In a table of 96 cases prepared by Kelynack,¹ 56 are given as occurring under the age of five years. The left kidney is more often involved than the right; sometimes the tumor is bilateral. Of 40 cases collected by Jacobi, 13 occurred in the right, 19 in the left, and 8 in both kidneys. The female sex is more frequently affected than the male.

The tumors may originate in the capsule, in the pelvis, or in the parenchyma of the kidney. Very often it is difficult to say where the growth had its starting point. It is possible that tumors of the retroperitoneal glands may grow into the kidney and simulate renal growths.

In the etiology of renal sarcomas, trauma seems to play a distinct role; this may explain the occasional tendency to the development of sarcoma in floating kidney. Metastasis to other organs occurs late in sarcoma of the kidney; the parts most often secondarily involved are the liver, lung, and abdominal lymphatic glands. Windle found the different parts involved in the following order of frequency: Liver, retroperitoneal glands, mesenteric glands, heart, diaphragm, adrenals, spleen, lungs, pancreas, intestines, pleura, renal vein, orbit, and elbow.

¹ *Renal Growths*, Edinburgh and London, 1898.

The simple sarcomas are rare in the kidney, but round-cell and spindle-cell tumors—the former usually highly vascular—have been observed. More common are sarcomas the histologic structure of which is very complicated; in addition to the ordinary sarcomatous elements, glandular tissue, nonstriped and striped muscle-cells, and sometimes cartilage are found. They have been called embryonal mixed tumors, adenosarcomas, rhabdomyosarcomas, and teratomas.

The histogenesis of these mixed tumors, all of which are malignant, is obscure. It is probable that some of those classed under this head are developed from suprarenal rests, and are best designated as hypernephromas; for a large group, however, other explanations must be sought. Birch-Hirschfeld¹ maintained that the adenosarcomas of the kidney were derived from displaced remains or “rests” of the Wolffian body. Busse,² on the other hand, believes that they spring from embryonal kidney-structure, and not from inclusions of remains of the Wolffian body.

These peculiar mixed tumors nearly always occur in children, and are very rare, although not unknown, in adults. For a time they grow slowly; and then, especially after a trauma, they take on rapid growth, attaining in the course of a few months the size of a child's head. The kidney is compressed by the tumor into a thin rim, or it may be divided into separate masses covering the poles of the tumor. The growth, even if large, tends to preserve the shape of the kidney, although the surface may be nodular. There is usually a capsule. The surface of section may be homogeneous and of a grayish-pink color; at times the tumor is composed of a conglomerate of encapsulated masses. Softening processes, cyst formation, and hemorrhage into the tumor frequently occur. Metastasis takes place late, and is rarely to the lymphatic glands; more often the tumor ruptures into veins and involves the lung secondarily. Even in the absence of metastasis, cachexia, as a rule, develops. The left side is more often affected than the right. In one-fifth (Jacobi) or in one-half (Paul) both organs are involved. The largest tumor known weighed 36 pounds; the average weight in 23 cases collected by Kelynack was 126 ounces (about 8 pounds).

Histologically, the picture is very complicated. Portions of the tumor may resemble carcinoma. This explains why we find it so commonly stated in the literature that renal carcinoma occurs early in life. Other portions have all the appearances of sarcoma. Sometimes the features are those of endothelioma. But neither true carcinoma nor true sarcoma occurs to any extent in childhood, and it is now definitely settled that the renal tumors of early life described under these names are of a different nature. They are *mixed tumors*, in that they are composed of several heterogeneous elements. A careful study reveals, as a striking feature, *tubular structures*, lined with epithelial cells and resembling the collecting tubules of the kidney. Where the tubules are typical a basement membrane is present, and then the appearance is that of an adenoma; excessive proliferation of the epithelial cells—and that these cells are actively proliferating is shown by an abundance of karyokinetic figures—may cause a filling up of the lumen and a versimilitude of carcinoma. There is, however, no true breaking through of the basement membrane, no true peripheral growth of epithelial cells, as in carcinoma; nor is there any evidence that the cells of the tumor spring from the adult epithelium of the kidney—a prerequisite if the tumor is to

¹ Ziegler's *Beiträge*, xxiv., 343.

² *Virchow's Archiv*, clvii., 346.

be called a carcinoma. Moreover, the tumor, as already mentioned, is sharply demarcated from the kidney; and, even if the capsule is burst by pressure, the tumor grows into the renal tissue in a way unlike that seen in true carcinoma.

A second feature is a *stroma*, made up of *round* or *spindle-cells*, surrounding the tubules. The amount of stroma varies, and may be so great as entirely to obscure the tubular element; there are even places in which the most careful study reveals only accumulations of round and spindle-cells, and the appearances are exactly those of sarcoma. It is highly probable that a large number of reports of sarcoma of childhood have crept into the literature as the result of an exclusive study of such fields. Usually the epithelial element and the cellular connective-tissue element are in inverse proportion in the different fields. In some tumors the sarcoma-like cells infiltrate between and into the gland-structures, causing a very complicated appearance, difficult of analysis.

In addition to these two elements, the majority of the renal sarcomas of childhood contain muscle-tissue of both the nonstriped and the striped variety. All gradations between striped and nonstriped muscle-fibers can be seen—the typical voluntary muscle with striation; the elongated spindle-cells striated about the nucleus; and fibers that resemble voluntary muscle in shape and staining reaction, but are without striation. Usually the nuclei are more numerous in the striped muscle-fibers than they are in normal muscle of children of the same age. It was the presence of voluntary muscle that led to the theory that these tumors are derived from misplaced embryonal tissues, particularly the parts of the Wolffian body, which, as Eberth pointed out, normally contains embryonal muscle-cells; but Busse maintains that the striped muscle-cells are developed by metaplasia from the nonstriped cells, and bases this opinion upon the following grounds: (1) The large number of transition forms. (2) The position and arrangement of the striped fibrillæ, which is not that of the somatic musculature, but that of nonstriped muscle. (3) The occasional presence of striation in places where only smooth muscle is found; this is the case in certain sarcomas of the cervix uteri and the vagina. (4) The discovery in the pregnant uterus of striated fibers, this being explained upon the basis of a metaplasia of the highly developed involuntary muscle of the uterus in pregnancy. Wilms and others, however, deny that the striped muscle-fibers in sarcomas of the kidney are produced by metaplasia from the unstriped, and maintain a derivation from the primitive myotome or muscle-segment of the early embryo.

In rare instances epithelial pearls, at times immediately surrounded by striated muscle-fibrillæ, are found in the adenosarcomas. These enigmatic structures have been explained as being the result of ectodermic inclusions on the one hand, or of metaplasia on the other. Islands of hyaline cartilage are sometimes present, and even ganglion-cells are said to occur.

The urine, as a rule, is free from albumin and blood; for this reason the diagnosis often remains obscure. The early metastasis produced by these tumors and the extreme youthfulness of the patients render operative removal of doubtful value.

Hypernephroma.—The kidney is the seat of another class of tumors which histologically presents wide variations, and which has been designated in the earlier literature as carcinoma, endothelioma, and angiosarcoma.

The true nature of the tumors was revealed only when Grawitz pointed out their probable origin from particles of suprarenal gland tissue included in the kidney. The close proximity of the two organs renders such inclusions in early fetal life possible. Both Klebs and Grawitz conclusively showed that the adrenal is sometimes entirely and sometimes in part contained within the kidney-capsule. Ordinarily the inclusions constitute small yellowish nodules, which may or may not be sharply circumscribed or surrounded by a capsule, and occasionally themselves include detached uriniferous tubules. Reference has already been made to these suprarenal rests, as they represent some of the lipomas that have been described as occurring in the kidney. These aberrant suprarenal rests are liable to proliferation and tumor growth, and to the new growths developed from them Cohnheim's theory of tumor formation very properly applies. Some other factor is, of course, necessary to explain why, after having been dormant for years, the bits of suprarenal tissue take on active growth; in some instances traumatism seems to have played a role. As a rule the tumors growing from adrenal rests—hypernephromas—are malignant, although they may be benign. They are usually found in persons past middle life (thirty-seven to sixty years), are more frequent in the male than in the female sex, grow rapidly, and give metastasis—not, however, as carcinomas do, to the regional lymph-glands, but by preference along the blood-stream, to the lung, the



FIG. 316.—Hypernephroma of the kidney.

liver, and, often very early, to the bones. The renal veins are generally involved, and even the vena cava may be attacked. The tumors vary in size; not rarely, they are very large, reniform, and compress or destroy the greater part of the kidney substance, although the general reniform outline is preserved. Sometimes they are separated from the kidney by a capsule, apparently formed by a condensation of the renal tissue; at other times the capsule of the kidney itself surrounds them. On section they present a whitish or yellowish appearance, are usually composed of an aggregation of nodules, and often show hemorrhagic or necrotic softening.

Pathologic Histology.—The tumor is composed of stroma and of cells. The stroma consists principally of a network of capillaries, in the meshes of which the cells are enclosed. As a rule the capillary endothelium is well preserved and the tumor-cells rest directly upon it. Sometimes the stroma is composed of wide bands of dense fibrous tissue, sending finer filaments into the interior of the meshwork, thus producing a distinctly alveolar appearance. Hyaline degeneration of the stroma occasionally occurs.

The appearance of the cells constituting the parenchyma of the tumor varies. In the central parts of the new growth the structure of the cortex of the suprarenal gland is often reproduced. The cells are large,

round or polygonal, and refractive; they possess a large amount of protoplasm, containing fat- and glycogen-droplets, or vacuoles if these have been removed in the hardening process, and a distinct cell-wall is usually present. The protoplasm is not entirely unlike that of sebaceous glands. The nucleus is large, stains well, is excentrically placed, and has a metachromatic nucleolus; sometimes giant cells of a multinuclear or a uninuclear variety are present. Mitotic figures are not common. The cells are often distorted by mutual pressure. Sometimes they are disposed in single or double rows, producing structures resembling tubular adenoma. This tubular appearance may also be brought about by an arrangement of the cells back to back on a thin septum of connective tissue or a capillary. At the periphery of the tumor the arrangement and character of the cells are often complex, and differ markedly from the conditions found in central portions. Sometimes groups of round cells which do not resemble adult suprarenal tissue are found; as Busse points out, they are similar to the cortical cells of embryonal adrenals. At times the cells are distinctly columnar in type. They may also grow in papillary masses into the alveolar spaces of the capillary meshwork. Cyst formation is rare; when present, it is usually dependent upon necrotic softening of the central portions of the cell-nests. Less often it is caused by dilatation of the lymph-channels, which may be so marked as to produce a lymphangiomatous appearance. In rare instances true epithelium-lined cysts are found; it must, however, be stated that good authorities deny the occurrence of true cysts. Blood-pigment is often present in the stroma of the tumor; occasionally nonstriated muscle-cells are also found.

Proper staining reveals the presence of glycogen in hypernephromas. Lubarsch considers the presence of this substance as characteristic of hypernephroid tumors; but this view is not tenable, as glycogen has been found in other new growths. As pointed out by Gatti and others, hypernephromas are rich in lecithin, for which, however, there is at present no microchemical reaction.

Whether these tumors are to be classed with the carcinomas or with the sarcomas cannot be definitely decided. If we make mere morphology the criterion, they sometimes deserve the name of the one and sometimes that of the other; if, however, we make histogenesis the basis, then the decision will rest upon the nature of the cells of the adrenal gland. If we consider them epithelial—as we must, in view of the researches of Weldon¹ and others, according to which the organ is derived from the cells of the protonephros—then the malignant tumors arising from adrenal rests are properly classed with the carcinomas. For the present, however, it is best to cling to the noncommittal term—hypernephroma.

It should be stated that not all authorities agree with Grawitz, Lubarsch,



FIG. 317.—Section from a hypernephroma (Kelly).

¹ *Quart. Jour. Micros. Sci.*, xxiv., xxv.

Gatti, Kelly, and others, who derive these tumors from adrenal rests; some look upon them as endotheliomas, or rather peritheliomas; others, as malignant forms of adenoma, derived from the uriniferous tubules.

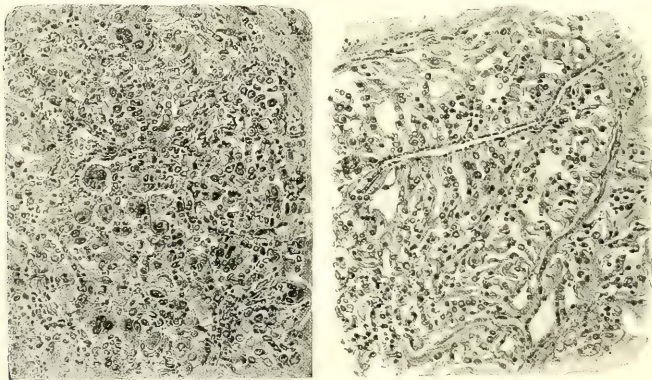
In conclusion, we may sum up the principal arguments advanced in proof of the adrenal origin of the tumors in question:

1. The situation of the tumor just beneath the kidney-capsule, this being the usual seat of displaced suprarenal rests.

2. The character of the cells, which resembles that of the cells of the adrenal cortex.

3. The presence of fat-droplets and glycogen in the protoplasm. Although glycogen is not a normal constituent of the suprarenal gland, it is always found in tumors of this organ (suprarenal strumas). We have already mentioned the fact that the presence of glycogen itself is not of great moment.

4. The metachromatic character of the nucleolus—that is, its property of staining differently from the nucleus—a condition never seen in renal



FIGS. 318, 319.—Sections from a hypernephroma. $\times 120$ (Kelly).

epithelium or true renal adenomas, but in adrenal rests and in the cells of the adrenal cortex.

5. The similarity of malignant adrenal and malignant renal tumors of so-called adrenal origin.

6. The absence of any transition between the tumor and the renal tissue.

7. The presence of giant cells, as in simple hyperplastic growths of the suprarenal glands.

8. The existence of an abundant capillary network, such as is seen in the cortex of the adrenal.

9. The tendency of the tumors to penetrate early into the veins.

10. The presence of lecithin in amounts closely approximating those characteristic of adrenal tissue.

The urine in malignant hypernephroma presents no characteristic feature; hematuria is, however, generally present.¹

¹ The following are some of the important articles on the subject of hypernephromas. As the majority of these have extensive bibliographies, no attempt has been made to give a

Carcinoma.—The occurrence of true carcinoma developing from the adult epithelial cells of the kidney is rare. It may grow from the pelvis and infiltrate the kidney, or it may begin in the organ itself, from the tubular epithelium (adenocarcinoma). The latter variety attains a large size and destroys the kidney-structure. Metastasis occurs late; there may, however, be perforation into the renal pelvis, with profound hematuria. If metastasis occurs, it is usually by a penetration of the tumor into the veins, with the production of tumor emboli.

Secondary cancer may occur in the kidney, just as in other organs; chorio-epithelioma (deciduoma malignum) not rarely gives metastasis to the kidney.

Adenoma.—A proliferation of the renal tubules resembling adenoma not rarely occurs in chronic interstitial nephritis, and is comparable to the proliferation of the bile-ducts in cirrhosis of the liver.

True adenomas are generally small, whitish, and multiple, and occupy the cortex. They may attain a large size and become cystic. Histologically two varieties can be distinguished—the *tubular* and the *papillary* adenoma. The latter, which is usually sharply encapsulated, differs from the former in the presence of club-shaped processes projecting into the lumen. The epithelial cells of adenomas are columnar in shape. Ricker¹ distinguishes a tubular adenoma and a trabecular cystoma; and also classes the adrenal tumors of the kidney among the adenomas. The trabecular cystomas are of a yellowish color, and are made up of cysts lined with fatty epithelium, resting almost directly upon capillary walls. It is probable that these cystomas are of suprarenal origin.

By excessive proliferation and bursting of the basement membrane adenomas may be transformed into carcinomas. In congenital cystic disease of the kidney adenomatous processes are held by some to play a part.

Cysts.—Cysts are common in chronic forms of nephritis, especially in the interstitial variety. They are small and multiple, and are situated under the capsule, sometimes at the junction of the cortex and pyramids. Their color is dark green. They vary in size from that of a wheat-grain to that of a cherry-stone, and are filled with a clear, yellowish, urinous fluid, or with a brownish colloid material. Etiologically they are retention-cysts, produced by constriction of the uriniferous tubules, the glomeruli of which still secrete.

A single cyst or several large cysts are sometimes seen in a kidney otherwise healthy. They project from the surface, and are intensely distended, either with an albuminous urine or a colloid material. They are lined with squamous epithelium. The walls show ridges indicative of a coalescence of smaller cysts. Their origin is not clear; they may be due to congenital or to acquired causes. A probable factor is obstruction of the collecting tubules, perhaps by concrement. It is also possible that an excessive activity of the epithelium, especially in the case of the colloid

complete list here: Grawitz, *Virchow's Archiv*, xciii., 39, 1883. Birch-Hirschfeld, *Lehrbuch der path. Anat.*, ii., Bd., 2. Hälfte, 838, 1895. Lubarsch, *Virchow's Archiv*, cxxxv., 149, 1894; cxxxvii., 191, 1894; *Ergebnisse der allg. Path. u. path. Anat.*, 1895, 2. Jahrgang (1897), 599. Sudeck, *Virchow's Archiv*, cxxxiii., 1893. Gatti, *Ibid.*, cxliv., 467, 1896. Kelly, *Ziegler's Beiträge*, xxiii., 280, 1898. Graupner, *Ibid.*, xxiv., 385, 1898. Buday, *Ibid.*, 501. Manasse, *Virchow's Archiv*, cxlii., 164, 1895; cxliii., 273, 1896; cxlv., 113, 1896. Hildebrand, *Langenbeck's Archiv*, xlvii., 225, 1894. Busse, *Virchow's Archiv*, clvii., 346, 377, 1899.

¹ *Centrabl. f. allg. Path. u. path. Anat.*, viii., 1897.

cysts, may be the cause. Some cysts probably originate in suprarenal rests; whether they are formed from adrenal tissue itself is, however, doubtful. According to Ricker, the renal tubules are sometimes included in adrenal rests; and it is these that develop into cysts.

Cystic Degeneration of the Kidneys.—*Polycystic Kidneys.*—This condition is usually congenital, but may be acquired. It is possible that the majority of cases of polycystic disease in adults are congenital, although the possibility of an acquired origin must be admitted. The kidneys are sometimes so large at birth as to constitute an obstacle to delivery. Congenital cystic disease of the kidneys is not rarely associated with a similar condition in the liver, and sometimes in the pancreas. It may occur in several members of the same family. The kidneys are enlarged, spongy, and composed of innumerable cysts of small size, varying from that of a cherry to that of a walnut. The cysts are separated by grayish-white septa, in which

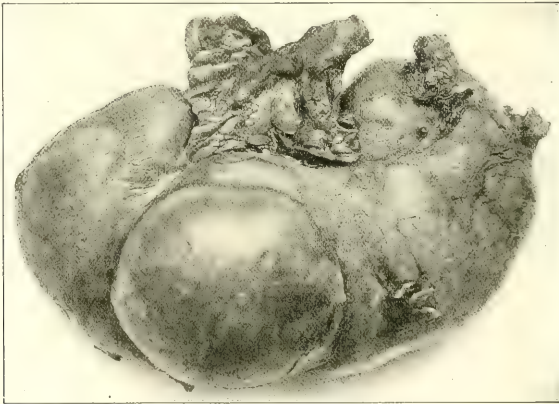


FIG. 320.—Single large retention-cyst of the kidney.

a few renal tubules may at times be found. The cysts are lined with pavement epithelium, and the fluid contains the usual urinary constituents. The *cause* of the cysts has been explained by Virchow as an inflammation of the papillæ—a papillitis leading to atresia of the ducts. The papillitis may be due to concrements in the tubules or to extension of inflammation from a pyelitis. It is sometimes associated with obliteration of the ureter or of the urethra, but these alone are only capable of causing hydronephrosis—not of producing cystic disease.

Others explain the condition as the result of faulty development. It is known that the secretory portions of the tubules and the collecting tubules have a different embryonic origin, the two “anlages” meeting in early embryonic life and becoming continuous. If the union is imperfect, or if there is an excess of one element over the other, cysts may afterward form, both from glomeruli and from collecting tubules. In one case Ribbert was able to demonstrate such a failure of union and to trace the development of cysts.

A third explanation, which may answer in some but not in all cases, is that the cysts are the result of a neoplastic growth; in other words, the cyst is a cystadenoma.

Cystic disease in adults may remain latent and be discovered only at autopsy, or it may remain latent for a long period and then suddenly lead to fatal uremia.

Dermoid Cysts.—Dermoid cysts may occur in the kidney, but are very rare.

Parasites.—It is scarcely necessary to mention that nearly all pathogenic bacteria that invade the body may be found in the kidney. The latter, in conjunction with other glands, is active in the elimination of micro-organisms, some of which may remain in the tissue and after death be found by staining or on culture.

Animal Parasites.—*Echinococcus*.—*Echinococcus*-cysts are far less common in the kidney than in the liver, and when they occur are usually of metastatic origin. In rare cases they are the result of direct extension from the liver. According to Neisser's statistics, the kidney is affected in 8.9 per cent. of all cases. Mosler and Peiper,¹ on the contrary, find the percentage to be only 2.8. Roscher² was able to collect 110 cases of renal hydatid disease, with 22 autopsies. The male sex is slightly more often affected than the female. The disease may occur at any age, but is most common between twenty and fifty. The cysts are due to the scolices of the *Tænia echinococcus*, a "tapeworm" inhabiting dogs. The cysts are multilocular, and vary in size from that of a child's fist to that of a man's head. In contour the tumors are rounded and smooth, and at times slightly lobulated. Their consistency varies. They may be situated at one or the other pole of the kidney, or may destroy the entire organ. They may also be located in the perirenal tissue. Rupture of the cyst may take place into the pelvis, with a discharge of daughter-cysts in the urine. This was found in 58 per cent. of the cases. In the absence of such rupture there are no urinary changes. Perforation may also occur externally, into the intestine, the stomach, the peritoneum, and the pleura.

Echinococcus-cysts are also found in cattle.³

Cysticercus cellulose has been found in the kidney. It is rare and unimportant.

Distoma Hæmatobium.—This flukeworm is not, as a rule, found in the kidney itself, but in the venous plexuses of the bladder. Its eggs, however, have been found in the renal parenchyma. The presence of the worm in the bladder leads to cystitis and pyelitis, and very often to stone formation, with atrophy and amyloid degeneration of the kidney.

Eustrongylus gigas is found in the pelvis of the kidney of man and the lower animals, and may cause destruction of the renal tissue. It produces—but not constantly—hematuria, and its eggs may be found in the urine.

Filaria Sanguinis Hominis.—The embryos of this worm are found in the kidney in chyluria, but do not, as a rule, produce any striking macroscopic change except a peculiar tallowy appearance of the surface of section.

¹ Nothnagel's *Specielle Pathologie u. Therapie*, Band vi.

² Ueber die *Echinococcuscysten* der Niere und des perirenal Gewebes, Inaug. Diss., 1898.

³ Ostertag, quoted by Melnikow-Raswedenkow, "Studien über den *Echinococcus alveolaris* sive multilocularis," 4. Supplementheft of *Ziegler's Beiträge*, 272, 1901.

Microscopically the embryos may be seen in the stroma, the parenchyma, and the walls of the arteries. They are also found in the urine.

Pentastomum denticulatum is the larva of the *Pentastomum tænioides*, a parasite found in the antrum and in the nasal and frontal sinuses of the dog, goat, wolf, horse, mule, and man. In the kidney it forms small cysts that undergo calcification.

THE PELVIS AND URETER.

Malformations.—The ureter and the pelvis may be absent; this is the rule when the kidney itself is absent. The pelvis may be small or defectively formed, especially in some cases of congenital cystic disease of the kidney. Its shape is peculiar in the different forms of horseshoe-kidney. The ureter may end blindly, or may be narrowed or obliterated for a part or the whole of its extent. Most frequently the upper end is thus affected. Under such circumstances the kidney is either atrophied or is the seat of hydronephrosis. Some cases of apparently congenital stenosis of the ureter are the result of ulceration due to the former passage of concretions.

Valve-like folds have been observed in the pelvis and ureter. Bending of the latter may also occur, particularly in cases of horseshoe-kidney in which the concavity points upward.

Doubling of the pelvis and of the ureter is not a rare anomaly, and is generally associated with a normally formed kidney. The two ureters may remain distinct throughout, emptying by separate openings into the bladder; or they may join in some part of their course to form one tube. In cases in which they empty separately the ureter with the lower opening is not rarely that connected with the upper of the two pelves, and, from having a longer course in the bladder-wall, is more subject to compression. Doubling of the ureter, which is not invariably associated with duplication of the pelvis, may be bilateral. Doubling is due to an abnormal sprouting of the primitive renal duct, close to its entrance into the cloaca. At times the ureter begins in three divisions, which join to form one tube. The ureter may open in abnormal places—in the prostatic urethra, the vagina, the uterus, the female urethra, the intestine, or the seminal vesicle.

Dilatation of the ureter and pelvis is caused by conditions interfering with the proper discharge of urine. The latter accumulates, and gradually distends the pelvis and calices, producing a condition termed *hydronephrosis*, or, if the distending fluid has the features of urine, *uronephrosis*. The ureter is also distended as far down as the obstruction.

The hydronephrosis may be partial, especially if there are two pelves and two ureters, only one being affected. When the obstruction is complete, the term closed hydronephrosis is applied; when incomplete, open. Hydronephrosis may be bilateral, but is more often unilateral, and is more common in the female sex. The condition is usually acquired, although it may be congenital. The causes of the former are foreign bodies in the urinary tract: Stones, blood-clots, parasites, and detached portions of tumors. Bernard¹ has found hydronephrosis in children as the result of the accumulation of masses of uric acid crystals in the ureter. Pressure upon the ureter from without, as by tumors, retroflexed or prolapsed uterus, and overfilled rectum or bladder, in a pelvis contracted by rickets or osteomalacia, may cause

¹ *Compt. rend. de l'Assoc. française d'Urologie*, 195, 1897.

hydronephrosis. Inflammatory processes in or about the ureter and pelvis, disease of the bladder involving the ureteral orifices, enlargement of the prostate, and stricture of the urethra are also causes.

In certain inflammatory conditions the mucous membrane of the pelvis, being movable, is drawn in front of the ureter and closes the opening after the manner of a valve. A somewhat similar valve-like effect may, according to Hansemann, be produced by traction upon the ureter itself. In cases in which the kidney is floating, torsion may cause obstruction and lead to hydronephrosis. If the hydronephrosis frequently recurs—intermittent hydronephrosis—the distention of the pelvis may become extreme. Hydro-

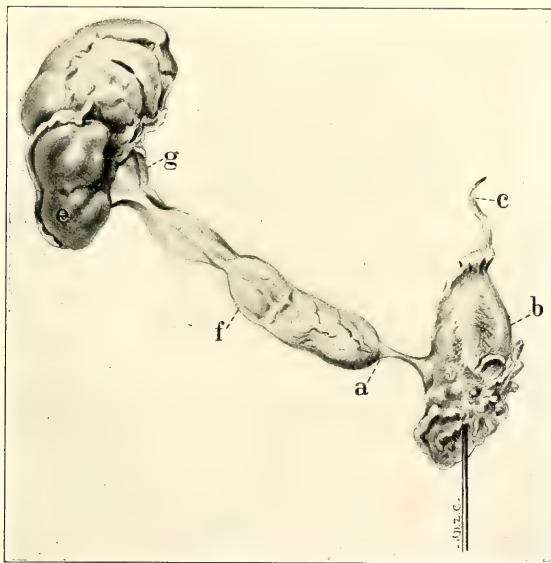


FIG. 321.—Congenital hydronephrosis from obliteration of the distal end of the ureter. The pelvis (g) and ureter (f) are dilated; from a onward the latter is obliterated; b, bladder; c, urachus; e, kidney.

nephrosis is also said to occur at times as the result of traumatism. At first the injury leads to an extravasation of urine—a so-called pseudohydronephrosis—which in turn compresses the ureter.¹ Monod,² however, considers all cases of traumatic hydronephrosis as cases of pseudohydronephrosis, the urine being in the retroperitoneal connective tissue and not in the pelvis.

Congenital hydronephrosis is most frequently due to stricture of the ureter. The stricture may be situated at any point, but is most common at the beginning; it may be total. Rarely, as already stated, the ureter is

¹ Wagner, *Centralbl. f. die Krankh. der Harn u. Sexualorgane*, vii., 1, 1896.

² *Ann. des mal. des organes g nito-urinaires*, x., 342, 398, 1892.

entirely absent. Another cause is anomalous opening of the ureter, and sometimes there is a valve in the ureter or pelvis. Absence of the urethra or congenital phimosis may also produce hydronephrosis. The ureter may likewise be compressed by an anomalous renal artery. In horseshoe-kidney, when the concavity is directed upward, the ureter in descending is compelled to make a sharp bend; for this reason horseshoe-kidney is occasionally hydronephrotic.

Hydronephrosis develops most readily when the obstruction is either intermittent or comes on slowly. An acute complete obstruction is not followed by hydronephrosis of any considerable degree, but soon leads to an arrest of secretion by counterpressure. Later, atrophy of the renal tissue develops. In cases of slowly developing hydronephrosis the accumulation continues until the counterpressure exceeds the pressure of secretion. The pyramids are flattened from pressure, and there may even be necrosis of the apices of the papillæ. Microscopically the epithelial cells in the early stages show cloudy swelling; later, fatty change; many are desquamated and disappear; but there is usually also evidence of attempts at cell multiplication. Coincidentally with the degenerative changes in the epithelium, the connective tissue increases and compresses the glomeruli and tubules. In advanced cases the kidney may be so altered that scarcely any renal tissue remains, and there is only a huge sac filled with fluid.

The fluid, which may amount to several liters, is urinous, but deficient in urea, chlorids, and phosphates; its specific gravity varies from 1002 to 1012. Epithelial cells from the pelvis and kidney, and sometimes red blood-corpuscles, are found. Albumin is at times present. In cases of long standing the fluid may become gelatinous. If the fluid becomes infected, pyonephrosis is developed. In such cases the fluid may be converted into a gruel-like substance containing cholesterin-plates.

Hyperemia.—An active hyperemia of the mucous membrane of the pelvis and ureter is found in cases in which irritants are eliminated in the urine and in inflammations; passive hyperemia occurs in thrombosis of the renal veins, and may lead to hemorrhage.

Hemorrhage.—Hemorrhage may be due to inflammation, passive congestion, infectious diseases, hemorrhagic diseases, injuries, stones, parasites, or tumors. The blood is discharged with the urine, either as a liquid or in the form of clots having the shape of the ureter.

Injuries, if severe, lead to rupture of the pelvis or ureter, and to the extravasation of urine. As the latter is sterile, no serious results are at first apparent; but there is a great tendency to infection of areas infiltrated with urine.

Edema.—Edema is seen in passive hyperemia and in inflammation.

Inflammation.—Inflammation of the renal pelvis is designated as pyelitis; that of the ureter as ureteritis. Pyelitis is usually due to extension of inflammation from the bladder or to the presence of stone in the pelvis; it may be produced by extension of disease from the kidney or by hematogenous infection of the pelvis itself. In rare instances it results from extension of inflammation from neighboring parts, as from a perinephritis. In the pyelitis secondary to cystitis the ureter is often slightly or not at all involved. It seems that the infectious agent is carried upward through the canal, and thus contaminates the urine in the pelvis rather than that the inflammation extends by strict continuity of tissue. The possibility of a

retrograde transport from the bladder to the pelvis has been demonstrated by Lewin.¹ The occurrence of an ascending pyelitis without a previous cystitis is also possible.

Pyelitis is usually bilateral, and may be catarrhal, suppurative, pseudomembranous, or gangrenous. In the first there are redness and thickening, and punctiform hemorrhages of the mucous membrane. The urine in the pelvis contains leukocytes and detached epithelial cells. In suppurative pyelitis the pelvis is more or less distended and filled with purulent urine. The mucous membrane is hyperemic, discolored, and thickened. Microscopically, round-cell infiltration, hyperemia, and desquamation of the epithelial cells are found. In cases of stone, and also in other forms of advanced suppurative pyelitis, ulceration, gangrene, and perforation of the pelvis may take place.

Pseudomembranous pyelitis (diphtheric pyelitis) is not rare in cases in which the urine is contaminated by virulent bacteria.

Acute pyelitis is usually due to the *Bacillus coli communis*. The urine is generally acid in such cases. If the cause of the pyelitis is extension from the bladder, the urine may in time undergo ammoniacal decomposition, occasionally with precipitation of phosphatic crystals on the mucous membrane. The urine is opaque, stringy, and of a dirty color, and has an offensive odor. In chronic pyelitis the mucous membrane is thickened and ridged; sometimes a papillary hyperplasia occurs, and rarely a peculiar cyst formation; at other times the mucous membrane is epidermalized, and becomes horny and shiny—a condition termed *cholesteatoma*.

Ureteritis, etiologically and anatomically, is similar to pyelitis.

Tuberculosis.—Tuberculosis of the pelvis appears as a miliary form and as a chronic caseous tuberculosis. The former is rare, and apparently the result of a hematogenous infection, which may appear to be primary. Chronic tuberculosis is either secondary to tuberculosis of the kidney or the result of upward extension of the disease from the bladder, seminal vesicles, prostate, or epididymis. The mucous membrane is infiltrated and thickened; caseation takes place and leads to ulceration. The ureter is involved by extension, its wall is thickened, and its lumen reduced and sometimes obliterated. The ureter is not rarely first affected at its point of entrance into the bladder, which is its narrowest portion; the disease may, however, begin above. Sometimes, instead of causing much thickening, the tuberculosis takes the form of an ulcer in the ureter. The canal may also be involved by the extension to it of cold abscesses from the vertebræ or the perirenal tissue.

The urine in tuberculosis is generally acid, and contains pus and blood, the latter sometimes being the first to appear. Tubercle bacilli are also present in the urine.

Tumors.—A comparatively frequent tumor in the pelvis is the so-called simple *villous papilloma*, a peculiar fluffy tumor more or less characteristic of the urinary passages. It is possible that some of these growths are really of inflammatory origin. Malignant papillomatous neoplasms (papillomatous epithelioma, Zottenkrebs) also occur, but, according to Kelly,² they are very rare, and have a tendency to invade the kidney. Sometimes carcinomas of the pelvis are associated with the presence of stones, and this has led to the

¹ *Arch. f. exper. Pathol. u. Pharmacol.*, xl.

² *Proc. Path. Soc. Phila.*, N. S., iii., 217, 1900.

belief that the stone plays a part in the production of the tumor. Lymphosarcoma of the pelvis of the kidney has been described.¹

In the ureter, a tumor resembling adenoma has been found; as the ureter has no glands, the tumor has been explained as springing from rests of the Wolffian duct. Primary carcinoma of the ureter occurs, but is rare. Cases have been reported by Hektoen² and by Voelcker.³

Cysts.—The pelvis, calices, bladder, and ureters, and even the urethra are at times the seat of multiple small cysts—*pyelitis*, *ureteritis*, *cystitis*, *urethritis cystica*—which have given rise to much speculation. There is still doubt as to their nature, since there are no true glands in the ureter and bladder. Von Brunn has, however, shown the existence of solid epithelial processes dipping down from the mucous membrane, from which the cysts may at times arise.

A parasitic origin has also been alleged for these cysts, von Kahliden claiming to have found a myxosporidium in the cells. Others attribute the cyst formation to proliferation of the subepithelial connective tissue, with elevation of the mucosa in such a way as to form an angle with the general surface. This angle becomes the starting point of the cysts.

Concrements, Stones, Calculi.—Nephrolithiasis.—Stones are often found in the pelvis and calices of the kidney. They are formed of material supplied by the kidney, and usually have an organic nucleus. They range from minute sand-like particles to large branching stones forming casts of the pelvis and calices. Sometimes several stones are present in the same kidney. The urate and oxalate of calcium stones are the most common. After ammoniacal decomposition of the urine phosphatic calculi may be deposited, or a phosphatic mantle may surround urate or oxalate stone. The stones cause pyelitis, pyonephrosis, and ulceration of the pelvis or ureter. From the latter the stones may perforate into the bladder, the intestines, the peritoneum, or the cellular tissue.

Parasites.—The *Distoma hæmatobium*, the *Filaria sanguinis hominis*, and the *Eustrongylus gigas* have been found in the pelvis. The eggs of the distoma are distributed in large numbers throughout the urinary tract, and are even found in the seminal vesicles. They appear in the urine as small pointed bodies, 0.12 mm. long and 0.04 mm. wide. Sometimes, instead of a terminal, there is a lateral projection. The filaria was first discovered in the urine by Wucherer, in Bahia. It produces hematuria and chyluria.

THE BLADDER.

Malformations.—The bladder may be entirely absent. In such cases the ureters open into the urethra or the vagina, or at the umbilicus.

Cases of multiple bladder have been reported; but in all probability there was only a single organ which had been divided by a septum into two or more parts.

Exstrophy or Extroversion.—This is a condition in which the anterior wall of the bladder is absent, the mucous membrane being directly continuous with the skin. It is usually associated with a deficiency of the anterior abdominal wall, and, not rarely, with other malformations, such as failure of union of the symphysis—epispadia in the male, and split clitoris

¹ C. P. White, *Trans. Path. Soc. London*, xlix., 178, 1898.

² *Jour. Am. Med. Assoc.*, June 6, 1896.

³ *Brit. Med. Jour.*, April 6, 1895.

in the female. Inguinal hernia may also be present. Exstrophy is most common in the male sex, and results from incomplete union of the urogenital clefts.

Diverticula.—Diverticula are usually of small size, and have been divided by Englisch¹ into (a) pockets—diverticula in which the wall contains both or only one of the muscular layers in addition to the mucous membrane; and (b) cells—those consisting of evaginations of the mucous membrane alone. The former are either congenital, or are formed on the basis of congenital or acquired weakness of the bladder-wall, as the result of increased intravesical pressure from stricture, enlarged prostate, or stone. Inflammatory processes attacking the submucous tissue may cause weakening of the bladder-wall at certain points and bring about diverticula. In a case of huge diverticulum, with hypertrophy of the bladder-wall, reported by Langer,² the origin was attributed to a congenital weakness of the muscular coat.

The bladder is sometimes divided by a septum (bipartite bladder), a condition that may be mistaken for multiple bladder.

Urachus.—The urachus may be patulous, in consequence of obstruction of the urinary outflow during fetal life. After birth a vesico-umbilical fistula forms, which discharges urine. If the canal is obliterated only in places, the intervening portions develop into cysts. Calculi are occasionally found in such urachal dilatations. A very interesting case of cyst of the urachus, forming a large abdominal tumor, has been reported by Ferguson.³ In the lower animals failure of closure of the urachus does not seem to be rare, and the dilatations have at times been looked upon as multiple bladders.

Malpositions.—The most frequent malposition is a descent of the bladder into the vagina—the so-called vaginal cystocele. It is usually associated with prolapse or other displacement of the uterus. In women inversion or prolapse of the bladder through the urethra may occur. Hernia of the bladder is infrequent. It is met with especially in the male sex, between the ages of forty and fifty, and is generally an inguinal cystocele.

The bladder may be prolapsed externally—ectopia of the bladder—if the abdominal or pelvic wall is defective.

Dilatation.—Dilatation is a common result of interference with the outflow of the urine by reason of the presence of stricture, enlargement of the prostate, stone, or paralysis of the bladder from spinal disease. It may reach enormous proportions. The largest amount of urine found by the writer was 88 ounces. If the dilatation is acutely produced, the wall is thin and translucent; if the obstruction is moderate and continues over a long period, the bladder-wall becomes hypertrophied.

Hypertrophy.—Hypertrophy of the bladder results from an increased demand upon its contractile power. The cavity may be normal, smaller than normal—concentric hypertrophy—or larger than normal—excentric hypertrophy. If the hypertrophy is marked, the interior of the bladder usually has a peculiar ribbed or lattice-like appearance, prominent ridges crossing each other in all directions, and leaving depressions which may be filled with concretions or may become the starting points of diverticula.

The increased functional activity is generally the result of obstruction to

¹ *Vortr. aus der ges. prakt. Heilk.*, April, 1894.

² *Zeit. f. Heilk.*, Bd. xx., Hefte 2 u. 3, 117.

³ *Trans. Phila. County Med. Soc.*, xx., 93, 1898.

the outflow; rarely it is of nervous or reflex origin. A congenital hypertrophy has been observed in children. Hypertrophy is a usual consequence of cystitis.

Atrophy.—Atrophy may be the result of prolonged distention or of old age. A fatty degeneration is said to occur in old age in the detrusor and sphincter muscles, and usually leads to incontinence of urine.

Paralysis.—Paralysis of the bladder may be caused by overdistention, prolonged compression, as by a pregnant uterus, and by lesions of the spinal cord. The bladder loses the power of contraction, becomes distended, and retention, with subsequent incontinence of urine, occurs.

Irritable Bladder.—This is a tendency to frequent contraction of the bladder and evacuation of the urine. If long continued, it may lead to hypertrophy of the bladder-wall.

Wounds and Rupture.—**Wounds** of the bladder may be due to stabbing, to firearms, to impaling upon sharp objects, and to falls, especially falls upon the perineum. They may also be produced by the surgeon, intentionally or inadvertently, and by prolonged labor, through pressure of the child's head. The effect depends to a large extent upon the seat of the perforation; if it is in a part covered by peritoneum, extravasation of urine occurs into the peritoneal cavity, and is speedily followed by septic peritonitis. In rare cases, however, the urine becomes encysted.

Rupture of the bladder may be due to fracture of the pelvis, a blow upon the abdomen, excessive straining, or the injection of fluid into the cavity. In rare cases it is spontaneous, from overdistention. Alcoholism seems to be a predisposing factor in rupture of the bladder, probably by causing a freer flow of urine, and by obtunding the sensibilities, so that the fulness of the bladder is not noticed. In cases of infiltrating tumors of the bladder itself or of tumors extending to the viscus, rupture is also possible. The point of the rupture is usually intraperitoneal, and may be vertical or oblique; when occurring in the extraperitoneal portion the tear is, as a rule, transverse.

Circulatory Disturbances.—**Hyperemia.**—Active hyperemia of the bladder is usually not demonstrable after death; during life there is a diffuse blush, the result of general capillary injection. Hyperemia is brought about by the presence of irritant substances in the urine; it may occasionally be seen in the bladder of women dead of puerperal infection.

Passive hyperemia is generally the result of pressure upon the vena cava, as by tumors or the pregnant uterus. If long continued, it may lead to varicose veins (hemorrhoids of the bladder), which have a tendency to bleed.

Hemorrhage.—In inflammation, passive congestion, varicose veins, hemorrhagic diathesis, injuries, stones, and tumors of the bladder, hemorrhage may occur into the bladder-wall or into the cavity. Tumors, even when small, often have a tendency to profuse bleeding, which in time may lead to profound anemia; and then a sudden hemorrhage, which otherwise would not be serious, may prove fatal. The bladder may in such cases be filled with a large blood-clot, as in an instance reported by the writer.¹

Amyloid Degeneration.—This is rare in the bladder, and is generally a part of a general amyloidosis; but occasionally, in connection with chronic inflammation, a local amyloid degeneration may develop.

¹ *Trans. Path. Soc. Phila.*, xviii., 304.

Cystitis.—The following varieties of cystitis can be distinguished: Acute catarrhal, phlegmonous or interstitial, diphtheric or pseudomembranous, gangrenous, and chronic cystitis. Inflammation of the bladder is practically always due to bacteria, but there are a number of factors which favor the action of the micro-organisms, viz., retention of urine, trauma, stone, exposure to cold, irritant qualities of the urine (which may themselves be due to bacterial activity, causing decomposition, or to the presence of poisons), and lesions of the spinal cord. The most common bacterium found in the bladder as the cause of cystitis is the *Bacillus coli communis*. But in the absence of any of the predisposing factors, this bacillus is incapable of producing a cystitis, as was shown experimentally by Melchior.¹ The *Proteus vulgaris*, it seems, has the power, independently of other factors, of producing nephritis. This is due to its ability to decompose the urine. According to Wertheim, the gonococcus may cause cystitis; as a rule, however, so-called gonorrheal cystitis is due to mixed infection. It is possible that the typhoid bacillus may produce a cystitis, and, naturally, the pyogenic organisms are capable of doing so. In rare cases the thrush-fungus is found as a disease producer in the bladder.

Pathologic Anatomy.—In ordinary catarrhal cystitis the bladder is usually empty and contracted after death. The mucous membrane may or may not be altered—generally there is some edema; the vessels are injected, and, if the inflammation is severe, hemorrhages and superficial ulceration are discernible. The favorite seats for the changes are the trigone and the urethral and ureteral orifices.

The lesions of acute catarrhal cystitis may subside or they may pass on to *chronic cystitis*. In this there is usually hypertrophy of the bladder-wall, involving particularly the muscular coat. The bladder-wall may be an inch or more in thickness. The interior of the viscus has a ribbed or trabeculated appearance. The veins are prominent, and the mucous membrane has a yellowish appearance, and is covered with shreds of mucus and urinary salts, especially in the depressions between the trabeculae. Occasionally the wall is thin and stretched, especially if the cystitis is connected with paralysis of the bladder from spinal disease.

Diphtheric or Pseudomembranous Cystitis.—This occurs in cases of advanced ammoniacal decomposition of the urine, particularly in connection with nervous paralysis of the bladder. The condition is at times found in women after labor. The false membrane is composed of fibrin and epithelial cells; in severe cases there is an extensive exfoliation of the mucous membrane of the bladder.

Gangrenous Cystitis.—This occurs especially in the cystitis accompanying paralysis of the bladder and in acute septic conditions. Grave injuries to the bladder and malignant tumors may also lead to gangrene. The trigone is usually affected, and is covered with a greenish slough surrounded by an intensely injected mucous membrane. Perforation may take place.

Phlegmonous Cystitis.—In chronic cystitis, especially when due to retention of urine from stricture or from enlarged prostate, the submucous tissue becomes at times the seat of a purulent infiltration, causing a bulging into the bladder, with eventual perforation—either internally, in which case an ulcer develops, or externally, with the production of a diffuse cellulitis—paracystitis.

¹ *Cystitis und Urininfection*, Berlin, 1897.

In small-pox a specific eruption (variolous cystitis) sometimes appears on the mucous membrane of the bladder. It is also possible that true diphtheria—*i. e.*, a false membrane produced by the Klebs-Loeffler bacillus—may occur in the bladder.

Cystitis Granularis.—This is a rare form of cystitis, characterized by the presence of small nodules in the mucous membrane, especially in the region of the neck of the bladder. Microscopically the nodules are composed of highly vascular lymphoid tissue.

Cystitis Cystica.—Reference has been made to this under the caption of Pelvis and Ureter; it is analogous to pyelitis and ureteritis cystica.

Effects of Cystitis.—Pain and difficult and frequent urination are the chief functional disturbances. In time cystitis leads to hypertrophy of the

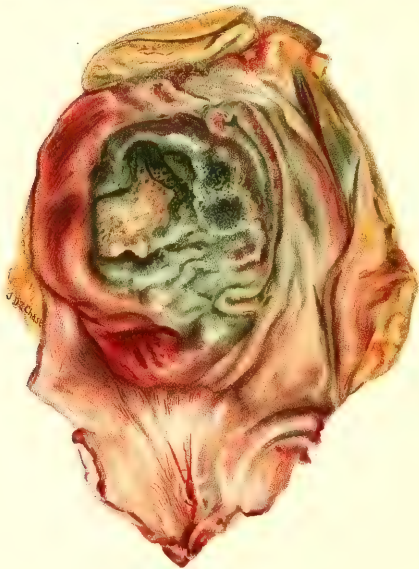


FIG. 322.—Gangrenous cystitis.

bladder-wall, except in cases in which the bladder has been permanently distended. The infection frequently ascends, causing pyelitis, pyelonephritis, and occasionally ureteritis. Extension to the surrounding tissues leads to *pericystitis* if the peritoneum is the part affected, and to *paracystitis* if the disease extends to the connective tissue about the bladder. Sometimes the term *pericystitis* is applied to both forms indiscriminately.

Inflammation occurring about the bladder has a special tendency to localization in the *cavum Retzii*, or space of Retzius, a small space in front of the bladder and external to the peritoneum. The inflammation is usually suppurative in character (*prevesical abscess*).

Ulceration.—Ulcers may form in the bladder during the course of a

severe cystitis, and in the case of stone, tuberculosis, or pressure by the child's head during labor. In the last condition the result is a vesicovaginal fistula. Rokitsansky also described a simple perforating ulcer, round in outline, and usually situated in the posterior and lower aspect of the bladder.

Cholesteatoma.—This is a condition, already mentioned in connection with pyelitis, in which the mucous membrane in places becomes thickened and keratinized. It is found in cystitis, especially that form due to stone.

The Urine in Cystitis.—In acute cystitis the urine is usually acid, contains pus-corpuscles, bladder-cells, and a trace of albumin. In chronic cystitis the reaction is generally alkaline; triple phosphates, ammonium urate, pus-corpuscles, bladder-cells, bacteria, and albumin are present. The urine has an offensive odor, is turbid or opaque, and often stringy or gelatinous from the action of the alkali (ammonium carbonate) on the pus. Sometimes the epithelial cells are destroyed and cannot be found in the urinary sediment.

Tuberculosis.—As a rule, tuberculosis of the bladder is a part of a urogenital tuberculosis; in rare instances it is directly secondary to tuberculous disease of the lungs or intestines.

In the first-named form the tuberculosis presents itself as an infiltration about the orifices—the mouth of the ureters and the neck of the bladder. Ulceration occurs early, extends to a varying depth, often undermining the mucosa, and occasionally perforating into the perivesical tissue or into the rectum. Tubercles may be seen on the floor of the ulcers. Cystitis and hypertrophy of the bladder are generally associated with the tuberculosis.

The starting point of a vesical tuberculosis which is a part of a urogenital tuberculosis may be the kidney—descending urogenital tuberculosis—or the prostate or seminal vesicle—ascending urogenital tuberculosis. The disease is most common in men under the age of forty, but may also occur at the extremes of life.

Syphilis.—Syphilitic ulceration has been described, but is exceedingly rare.

Tumors.—There is a marked tendency on the part of tumors of the bladder to be polypoid. A mucous polyp occurs not rarely, but it is probable that it has an inflammatory origin, and is therefore not a true tumor. **Fibroma**, **myxoma**, and **leiomyoma** are found; **sarcoma** is rare, is usually large in size, and multiple, situated about the orifices, and sometimes infiltrates the bladder-wall, causing an enormous thickening.

A rather common tumor is the **soft** or **villous papilloma** [Zottengeschwulst] a pediculated or sessile growth, having its most frequent seat in the region of the trigone. It may be small and slender, projecting like a tendril into the bladder, or it may be a large, cauliflower-like mass. The individual villi consist of a capillary loop, covered with a small amount of connective tissue and several layers of cylindric epithelial cells, resembling in arrangement the epithelium of the bladder. Sometimes these tumors occupy an extensive area along the surface of the urinary tract. Bleeding is very common, and may lead, as already stated, to grave consequences. Not rarely villi become detached and appear in the urine. Anatomically the tumors are benign, but they have a tendency to recur after removal, and occasionally seem to become malignant—*i. e.*, carcinomatous; they also may ulcerate. Cystitis generally accompanies the presence of this as well as other tumors of the bladder.

Carcinoma.—Squamous epithelioma is the usual type of malignant epithelial growth. It may be villous or infiltrating, the latter causing marked thickening of the bladder-wall. Horny change is rare, as is also metastasis.

Secondary carcinoma as the result of extension of uterine or vaginal carcinoma is comparatively frequent in the bladder of women. The interesting statement has been made by Rehn, Leichtenstern, and others that workers in fuchsin factories are especially liable to cystitis and bladder-tumors. In one case the new growth was examined and found to be sarcoma.

Cysts.—Reference has been made to *cystitis cystica*. Other cysts are rare; usually they represent diverticula. Dermoid cysts may occur in the bladder.

Parasites and other Foreign Bodies.—Various pathogenic and nonpathogenic bacteria, yeasts, and the thrush-fungus (*Oidium albicans*) have been found in the urine, the two last especially in diabetes. The thrush fungus may cause a white deposit on the mucous membrane. Among animal parasites, the *Distoma hæmatobium*, the *Filaria sanguinis hominis*, and the *echinococcus* should be mentioned. Cysts of the last-named may be found free in the bladder. A fungoid tumor, apparently caused by the distoma, has been described by Meinecke. *Oxyuris* and *ascaris* may enter the bladder in cases of vesicorectal fistula.

Various inanimate *foreign bodies* may be found in the bladder—fragments of catheters, hairpins, pipestems, spicules of bones, bullets, etc. Such objects may become a nucleus for stone formation.

Concrements; Calculi; Stones.—Vesical calculi are very frequent, although they do not appear to be encountered as often as formerly. They vary in number, size, shape, consistence, and chemical composition. Usually there is only one, but sometimes they are exceedingly numerous, and the writer has seen the bladder nearly filled with calculi.

In size stones vary from sand-like particles to masses the size of a chicken's egg—the average is from 1 to 2 inches, the average weight being from 2 drams to 1 ounce. The shape of single stones is usually a flattened oval; a multiplicity of stones produces flattening of opposing surfaces, as in the case of gall-stones. Hardness varies with chemical composition—the mulberry (calcium oxalate) stones are the hardest, the phosphatic the softest. Calculi may be composed throughout of the same substance, or they may consist of alternating layers differing in composition—alternating calculi.

Etiology.—Some of the stones found in the bladder are of renal origin. This is particularly true of urate and calcium oxalate stones. After their migration to the bladder they may become invested with a deposit of phosphatic material. Regarding the formation of stones, whether in the kidney or the bladder, it is now established that some sort of nucleus or matrix is requisite. This matrix is usually organic—an albuminous or mucinous coagulum derived from the mucous membrane. Foreign bodies may constitute the nucleus, although it is likely that they do so only after having become entangled in an albuminous substance—the real matrix.

The drinking of limestone water, diet, hereditary predisposition, etc., are supposed factors in lithiasis.

Stones are most common in the male sex, and in early life, by far the larger number occurring under the age of twenty; many are found in children.

Situation.—The majority are found in the lowest part of the bladder

(bas-fond); the neck, above the pubis, and behind the prostate are other favorite seats. The stone may be free or encysted.

Effects.—These are pain, dysuria, frequent micturition, hematuria, cystitis, hypertrophy of the bladder, pyelitis, and pyelonephritis.

Varieties of Calculi.—*Uric-acid calculi* are small, hard, grayish-yellow or reddish-brown, and multiple. On section they are smooth and concentrically striated. They originate in the kidney substance or the renal pelvis. *Urate calculi* are composed of sodium, potassium, or ammonium urate, but are often encrusted with calcium oxalate or triple phosphate. *Phosphatic calculi* are whitish, grayish-white, or clay-colored, soft and crumbling, especially those composed of ammoniomagnesium phosphate. Calcium phosphate calculi are a little harder. While pure phosphate stones are common, combinations with other excrementitious materials, as with urates or calcium oxalate, often occur. *Calcium-oxalate calculi* constitute the so-called mulberry calculi. They are hard, brownish, of medium size, spheroidal, with a nodular surface, and are usually of renal origin. Not rarely they have a mantle of triple phosphate. *Calcium-carbonate calculi* are very small, white, hard, and multiple. *Cystin calculi* are rare, of small size, translucent, waxy, yellowish, turning greenish on exposure. *Xanthin calculi* are among the rarest bladder stones; they are smooth and of a reddish-yellow color. *Indigo* seldom forms independent stones, but may be associated with other material. *Biliary calculi* have been found in the bladder in cases in which a fistula existed between the gall-bladder or bile-passages and the urinary tract.

THE URETHRA.

Malformations.—*Absence* of the urethra is usually fatal to the child before birth. Congenital stricture, as a rule, depends on the presence of a membranous diaphragm; in rare instances the entire urethra is converted into a fibrous cord. Sometimes the roof, sometimes the floor, of the urethra is defective, the malformations being termed epispadia and hypospasia respectively. *Doubling* of the urethra is rare, and is generally associated with doubling of the penis. In a case observed by the writer (see Fig. 323) there was a single penis, with two urethras but only a single anterior opening. Sometimes three openings exist; they must be looked upon as congenital fistulas.

Wounds and Ruptures.—Surgical wounds, if longitudinal, heal readily without bad effects; transverse wounds, owing to retraction of the proximal portion, heal by granulation and the eventual formation of a stricture. Accidental injuries may be produced by the passage of instruments (false passages) and other foreign bodies and by external violence. Subcutaneous rupture is most frequent in the perineal portion; the result is extravasation of urine. In women the urethra may be ruptured during labor.

Hemorrhage.—This may be due to injuries, inflammation, rarely to coitus. The blood is bright red, is discharged with the first urine passed, sometimes in the shape of clots conforming to the urethra.

Urethritis.—The most important inflammation is *specific* or *gonorrheal urethritis*—gonorrhea or blennorrhea, an inflammation due to the gonococcus. The male urethra, owing to the fact that it in part subserves the sexual function, is much more liable to gonorrheal infection than the female urethra. The disease is acquired in sexual congress, the gonococci in the vagina entering the male urethra to a variable depth. While other modes of infection are possible, they are exceedingly rare. The gonococcus is found in the purulent discharge that escapes from the urethra. It is a biscuit-shaped or coffee-bean-shaped diplococcus, occurring in groups attached to polymorphonuclear leukocytes or outside the cells. The incubation period is from three to five days.

Pathologic Anatomy.—The gonococcus produces an inflammation of the mucous membrane which is at first superficial and confined to the anterior region of the urethra, in particular to the fossa navicularis (anterior urethritis). In the mucous membrane the gonococci are found within and between the epithelial cells and within leukocytes that have emigrated into the epithelial layer. After a short time the bacteria penetrate into the subepithelial connective tissue, in which numerous leukocytes containing bacteria are found.

The epithelial cells themselves become swollen and in places are shed.



FIG. 323.—Doubling of male urethra.

The discharge is a thick, yellowish, acrid pus, occasionally blood-tinged, and contains polymorphonuclear leukocytes and a few epithelial cells. The gonococci are present in great abundance, chiefly within leukocytes.

Chronic gonorrhea is localized especially to the urethral glands (glands of Littre) in the posterior portion of the canal (posterior urethritis, gleet). The subepithelial layers are chiefly involved, and are the seat of round-cell infiltration and proliferation of the fixed cells, the ultimate result being a new formation of connective tissue and contraction (stricture of the urethra). The original epithelial cells suffer degeneration and desquamation, their

place being taken by squamous epithelium, which may become so thickened as to form papillomatous projections.

The regional lymph-glands—those of the groin—are rarely affected; if they suppurate, the pus is usually sterile; at least it is free from gonococci. Epididymitis, prostatitis, peri-urethral abscess, cystitis, and pyelitis are complications produced by extension of the inflammation by contiguity. Con-

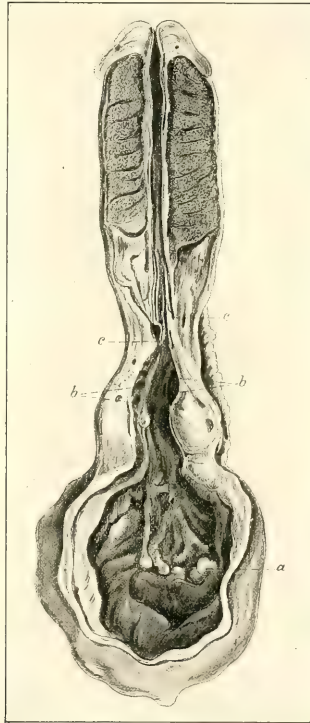


FIG. 324.—Extreme contraction of a stricture of the urethra in a patient nineteen years of age: *a*, diverticulum of the bladder; *b, b*, dilatation of the prostatic ducts; *c, c*, false passages (after Dittel).

junctival, oral, and rectal gonorrhea are due to the direct implantation of bacteria upon the respective mucous surfaces.

Gonorrhea may also cause lesions at a distance, the infection being conveyed by the blood—arthritis, tenosynovitis, endocarditis, myocarditis, pleuritis, peritonitis, neuritis, myositis, and myelitis, have all been described. They usually depend on mixed infection, but the gonococcus has been found as the sole instigator of the inflammation in a number of them. It has so

far not been demonstrated in the nervous complications. In endocarditis the gonococcus may be present in the blood on culture (Thayer and Blumer).¹

Gonorrhea is said to predispose to tuberculosis of the testicle.

There is also a *nonspecific urethritis* due to trauma, to the entrance of irritant substances, etc. Gonococci are not found, and the inflammation soon subsides. In women such nonspecific inflammations not rarely accompany puerperal inflammations. Chronic inflammation in women often leads to epithelial hyperplasias, which, when at the meatus, give rise to the so-called urethral caruncle.

Diphtheric or croupous urethritis is rare; it is at times produced by irritant injections into the urethra.

Strictures of the Urethra.—Strictures are most frequent in the bulbomembranous portion of the urethra, but are also very common in the anterior two and one-half inches of the penile urethra. The older, the more fibrous and resilient is the stricture; sometimes it causes nearly complete obliteration of the canal. Several strictures may be present at the same time. As a sequel of gonorrhea, stricture appears quite late—usually not before a year after the acute attack; while after wounds and injuries strictures form very promptly.

Effects of Stricture.—These are dilatation of the urethra and neck of the bladder behind the stricture; hypertrophy of the bladder, and often cystitis, ureteritis, and pyelonephritis. Peri-urethral abscesses and urinary infiltration are also not rarely produced.

Tuberculosis.—When this is part of a descending urogenital tuberculosis it has its seat usually in the prostatic urethra, but the whole canal may be involved. Urethral tuberculosis may be an extension from tuberculosis of the penis. In women lupus of the vulva may implicate the urethra.

Syphilis.—Chancre is occasionally found, stricture resulting from its healing. Gummas are also possible in the urethra. *Chaneroid* is not rare.

Leprosy.—Leprous lesions sometimes occur in the urethra.

Tumors.—Tumors of the urethra are not common. A papillomatous hyperplasia occurs in connection with gonorrhea. Adenomatous hyperplasias, often cystic, are also found. These varieties of tumors are most common in the female sex.

Carcinoma of the urethra is a rare growth. It occurs in advanced life, and usually takes the form of squamous epithelioma. Adenocarcinoma may develop from Cowper's glands. Carcinoma may invade the urethra secondarily, extension occurring from the glans penis or the prostate. Sarcoma is exceedingly rare, and is usually secondary to sarcoma of the penis.

Foreign Bodies and Concrements.—A great variety of foreign bodies may be introduced into the urethra from without. In rare cases spicules of bone detached from the pelvis in case of necrosis lodge in the canal.² Calculi may be found in the urethra itself behind strictures; ordinarily, when found there they come from a source higher up.

THE MALE SEXUAL ORGANS.

Malformations.—Total absence of all sexual organs is seen only in cases of extreme malformation. Imperfect formation, especially of the external genitalia, may coexist with an otherwise fair bodily development.

¹ Bull. Johns Hopkins Hosp., 1896.

² Schmidt, Münch. med. Woch., 1898, 917.

Hermaphroditism.—The origin of the generative organs from a primarily undifferentiated rudiment explains the possibility of the development of both male and female sexual glands in the same individual. The coexistence of testicles and ovaries in the same person constitutes *true hermaphroditism*—hermaphroditismus verus. It is rare, and is generally of the type known as hermaphroditismus verus lateralis, in which there is an ovary on one side and a testicle on the other. In *false hermaphroditism*—pseudohermaphroditism, hermaphroditismus spurius—the individual is unisexual, and has either ovaries or testicles, but the genital canals and external genitalia partake of the features of both sexes. In such cases the secondary sexual characters and the general habitus of the individual cast a shadow of ambiguity upon the sex. The majority of pseudohermaphrodites are males.

The Testicles.—*Absence* of both testicles—*anorchism*—is rare, and involves the nondevelopment of the secondary sexual characters, particularly smallness of the larynx. *Absence* of one gland—*monorchism*—leads to hypertrophy of the other, the individual usually possessing proper masculinity. Smallness—*microrchism*—is seen especially in cases of nondescent of the testicles. Fusion of the testicles—*synorchism*—is extremely rare.

Nondescent of the testicle—*cryptorchism*—is moderately common. The testicle may be retained in any part of its course from the region of the kidney to the scrotum, the condition generally being unilateral. The causes of cryptorchism are various: adhesion of the testicle to the abdominal structures, smallness of the inguinal ring, weakness of the gubernaculum testis, etc. The undescended testicle is small, but histologically well formed and capable of elaborating spermatozoa. It is liable to inflammation and to malignant change. Hernia is often present. The testicles may be entirely displaced—*ectopia testis*—occupying sites out of the line of normal descent, as, *e. g.*, in the perineum. Inversion of the testicle sometimes occurs in the scrotum.

The External Genitalia.—*Absence* of the penis is very rare. Doubling is occasionally observed.¹ The prepuce may be redundant or absent. In the former case it projects in a snout-like fashion, and cannot be retracted—congenital phimosis.

The most important developmental anomalies are *hypospadias* and *epispadias*. In the former the lower portion of the penis is defective and the urethra opens on the floor of the organ. In extreme cases the penis resembles the clitoris; the scrotum is cleft, and the condition is one of pseudohermaphroditism. In epispadias, which is rarer, the urethra opens on the upper surface of the penis. A congenital transverse division of the glans has been described.

THE TESTICLE.

Wounds.—Wounds of the testicle heal with the formation of a granulation tissue, the exact origin of which has been a source of contention. Maximow has shown,² by animal experiments, that this tissue is descended from the connective-tissue cells and the fibrillar tissue of the walls of the seminiferous tubules. A considerable share is also taken by the mysterious interstitial cells (*Zwischenzellen*) of the testicles.³ There is, however, no new formation of seminiferous tubules.

Inflammation may attack the testicle or the epididymis, or both, or the tunica vaginalis.

Etiology.—Orchitis and epididymitis are due: (a) To extension of inflammation of the urethra along the vas deferens. This mode of infection is common in gonorrhea and in inflammation following instrumentation. (b) To hematogenic infection, as in mumps, typhoid fever, small-pox,

¹ Lange, *Ziegler's Beiträge*, xxiv., 223; Keppel, *N. Y. Med. Jour.*, lxxviii., 710, 1898.

² *Ziegler's Beiträge*, xxvi., 230.

³ These cells, situated in the intercellular connective tissue, are large, polygonal, protoplasmic elements, containing fat droplets, pigment granules, and occasionally crystals (Klincke's crystalloids). There may be one or two nuclei. The cells have been considered by some as epithelial in nature, derived from remains of the Wolffian body, and by others as belonging to the connective-tissue type. The latter is probably the correct interpretation. A peculiar fact has been pointed out by Finotti (*Langenbeck's Archiv*, lv., 1897); namely, that in undescended testicles there is a marked increase in the *Zwischenzellen*, which may be so extreme as to compensate for the atrophy of the testicle that usually takes place. In such testicles the interstitial cells generally undergo a fatty metamorphosis. Finotti looks upon the cells as rudimentary structures, not of connective-tissue origin, which remain from embryonal life.

scarlet fever, influenza, malaria, and ulcerative endocarditis. According to Kocher and others, the orchitis of mumps is not hematogenic, but is due to urethral infection. (c) To traumatism.

Pathologic Anatomy.—In acute orchitis the testicle is enlarged and tense, owing to the swelling of the organ in its tight capsule. An effusion into the tunica vaginalis is generally present. Hyperemia and round-cell infiltration into the intertubular tissue characterize the condition histologically. Occasionally abscess forms, which may become encapsulated and inspissated, or may perforate externally, producing the so-called benign fungus. Chronic orchitis is a common sequel of the acute, and is marked by an overgrowth of fibrous tissue and atrophy of the tubules; often it is accompanied by an adhesive periorchitis. Suppression of the testicular function is the usual result. Such a fibrous inflammation may be produced by syphilis.

The cause of the orchitis of mumps is not known. Although usually mild, the inflammation may lead to atrophy of the testicle. Orchitis in typhoid fever may be due to the typhoid bacillus, the infection being usually hematogenic, although infection by way of the urethra is possible. Several Russian observers have found decided histologic changes in typhoid fever and other infectious diseases. Eshner¹ states resolution to be the rule in typhoid fever, although atrophy or suppuration sometimes follows.

Epididymitis as an independent infection is generally due to gonorrhea or to septic infection of the urethra by instruments, etc. The epididymis is swollen, stony hard, and tender. Microscopically, the intertubular tissue is the seat of round-cell infiltration; the blood-vessels are distended, and the lumen of the tubules is filled with desquamated cells, exudate, and leukocytes. Small abscesses may form.

Tuberculosis.—Tuberculosis of the testicle and epididymis is common. It may be a part of a general urogenital tuberculosis, the vas deferens, seminal vesicles, prostate, bladder, and ureter being also involved; or it may be primary in the sense of the testicle or the epididymis being the first organ of the urogenital tract to be affected. Only in rare instances is there no other tuberculous focus in the body. In such cases of strictly primary genital tuberculosis the lesion is usually in the epididymis. The infection of the testicle and epididymis is either hematogenic or extends along the vas deferens from the prostate and bladder. Urethral infection, although possible, is rare. Traumatism and gonorrhea seem to act as predisposing causes. Not rarely testicular tuberculosis gives rise to a tuberculous meningitis or to general miliary tuberculosis. The disease is usually bilateral, and affects especially young adults.

Anatomically, a localized and a diffuse tuberculosis are recognizable. In the former, one or more circumscribed caseous nodules are visible in the epididymis or testicle. In the latter, as pointed out by Coplin,² the entire organ is permeated by closely approximated miliary tubercles, the larger ones being visible to the naked eye. In the epididymis, the process begins in the walls of the tubules of the globus major, and quickly causes obliteration of the lumen by desquamation of the epithelial cells and the entrance of leukocytes. The tubercles are rich in giant cells and tend to early caseation. Extension to the testicle occurs after a time.

In the testicle the process, as a rule, commences in the tubules (canalicular tuberculosis); in exceptional instances, in the interstitial tissue. The elastic tissue, as

¹ *Phila. Med. Jour.*, i., 949, 1898.

² *Proc. Path. Soc. Phila.*, I., New Series, 267, 1897-98.

Federmann¹ has shown, disappears wherever the tuberculous granulation tissue invades the tubules, even before any caseous necrosis has taken place. In the caseous areas there is also no elastic tissue, or, at the most, only a few fibers, which are either scattered irregularly or surround the caseous zones. Caseation arrests the destruction of the elastica, the latter apparently suffering more from the ferment action of the tuberculous granulation tissue than from the necrotic process. The testicle becomes enlarged and is the seat of separate nodules, the centers of which are often broken down. Giant cells, usually in enormous numbers, are scattered throughout the affected part, and caseous necrosis is marked. The process is apt to extend to the tunica vaginalis, leading to hydrocele, or more often to adhesive inflammation of the two layers. Perforation of the scrotum, with production of fistulas, finally takes place.

The occurrence of hematogenic infection of the testicle renders it *a priori* likely that in a tuberculous patient tubercle bacilli may be carried to an apparently normal testis. This was maintained by Jani,² Walther³ and Jaechh,⁴ however, did not find any bacilli in normal testicles. Nevertheless, the most recent investigation—that of Nakarai⁵—demonstrates that bacilli may be present in the normal testicle and epididymis of a tuberculous individual. The number of bacilli, however, is insignificant, and the transmission of tuberculosis to the offspring through the semen is a doubtful possibility.

Syphilis.—The testicle is one of the organs most liable to syphilitic disease. The epididymis is less often involved. Two types of the disease may be distinguished: (*a*) a diffuse fibrous inflammation, and (*b*) a gummatous form. The first presents nothing characteristic anatomically. It is

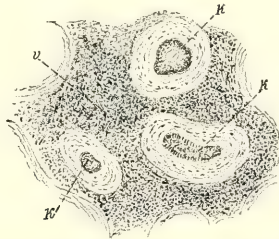


FIG. 325.—Gummatous orchitis: *k*, atrophic seminal canals, with hyaline walls; between them is gummatous granulation tissue, at *v* converted into caseous material (Kaufmann).

marked by an increase of connective tissue in the septa, with atrophy of the tubules. The organ is hard and slightly enlarged. The history and the associated conditions alone decide the syphilitic nature of the process.

Gummatous orchitis (syphilitic sarcocoele) is characterized by the formation of nodules, irregular in outline, generally situated in the anterior portion of the testicle, and surrounded by dense bands of fibrous tissue and compressed tubules, from which other bands spread in a radiating manner. Federmann⁶ has pointed out that, differing from tuberculosis, in syphilis the elastic tissue of the testicle remains intact. This constitutes a valuable differential sign between the two processes. In fibrous orchitis due to syphilis or to any other cause the elastic tissue is not alone preserved, but also assumes a peculiar nodular appearance, which is never found in the ordinary form of tuberculosis. It has been maintained that a peculiar hyaline transformation of the wall of the tubules is characteristic of syphilis, but Federmann discovered a similar change in tuberculosis. If caseation occurs, calcification is prone to take place. The affected testicle usually becomes very hard, and is sometimes converted into a large

¹ *Inaug. Diss.*, Göttingen, 1900.

² *Ziegler's Beiträge*, xvi., 2.

³ *Ziegler's Beiträge*, xxiv., 327.

⁴ *Virchow's Archiv*, ciii., 1886.

⁵ *Virchow's Archiv*, cxlii., 101.

⁶ *Loc. cit.*

tumor of cartilaginous consistence. The tunica albuginea is thickened; the tunica vaginalis, adherent. The skin is rarely involved, and fistulas do not form, as a rule.

Leprosy.—Leprous nodules, rich in bacilli, occur both in the testicle and in the epididymis. **Glanders.**—The human testicle is seldom if ever spontaneously affected with glanders. In experimental glanders, however, the testicle seems to be especially predisposed to the disease—a fact of which use is made in diagnosis (Strauss' phenomenon). **Leukemia.**—Leukemic infiltration of nodular or diffuse form has been observed in the testicle.

Tumors.—**Fibromas** occur in the form of small nodules springing from the tunica albuginea or the rete testis; they are also found in the spermatic cord. **Lipoma** is rare, and occurs particularly in the cord. **Myxoma.**—As an independent tumor, this is not common. It is more often seen combined with fibroma, lipoma, or sarcoma. **Myoma.**—Both nonstriated (liomyoma) and striated (rhabdomyoma) have been found. The latter is usually situated at the point of attachment of the gubernaculum testis. **Osteoma** is rare. Ossification sometimes occurs in chondromas and sarcomas.

Chondroma or Enchondroma.—Pure cartilaginous tumors are uncommon. They are usually small, oval tumors, smooth, rarely nodular, and hard. Sometimes they attain a large size—up to 1 kg. The cartilage is either sharply circumscribed, in the form of translucent, hyaline islands, or merges gradually into the surrounding tissue. Mucoid degeneration, calcification, and ossification may occur. Metastasis to the lungs sometimes takes place. Nothing definite is known as to the source of the cartilage. The tumor is most common in adult life, between the ages of twenty and forty years, but also occurs in children. A history of injury is often obtained. Cartilage is frequently found in other testicular tumors.

Sarcoma.—All varieties of sarcoma are possible in the testicle, but the round-cell and spindle-cell forms are the most frequent. The first is soft; the latter hard and generally mixed with other tissue elements (*mixed tumor of the testicle*). Sarcoma may appear in the form of separate nodules or may substitute the entire testicle. Degeneration, necrosis, hemorrhage, and cystic change are common. Glycogen infiltration has also been observed. Cysts usually result from dilatation of seminiferous tubules, and are filled with a grayish, gelatinous material. The lining of the cysts may become keratinized. Sometimes there is a new formation of tubules: the tumor then is termed adenosarcoma, or cystadenosarcoma. Such growths are with difficulty distinguished from carcinoma. A perplexing variety of sarcoma is the angiosarcoma of endothelial or perithelial type. In the latter the sarcoma cells often resemble epithelium very closely. They surround the blood-vessels, either directly or with an intervening covering of connective tissue, and sometimes form papillary processes. A plexiform arrangement is also common. As to the origin of sarcoma, Hanseemann believes that the large-cell varieties spring from the peculiar Zwischenzellen (interstitial cells) of the testicle. Cartilage is often present. Metastasis of simple sarcoma is infrequent, but the complex ones give metastasis to the lymph-glands, the liver, etc.

Adenoma.—Adenoma springs from the seminiferous tubules, and may be solid or cystic. Accordingly as the cysts are filled with a clear, mucoid fluid, generally devoid of spermatozoa, or with a cheesy material, the tumors

are designated as *cystadenoma mucosum* and *cystadenoma atheromatosum*. In the latter the cysts are lined with a thick epithelium, partly keratinized; the contents are yellowish and concentrically striated. The lining of the former is a simple or stratified cylindric or ciliated epithelium. Allusion has already been made to the combination of adenoma with sarcoma. Cartilage and muscle-cells, especially the nonstriated, are often present.

Carcinoma.—This has usually been considered a tumor of frequent occurrence, but there is no doubt that endothelial and perithelial growths have often been confounded with it. The tumor causes great enlargement of the testicle, perforation of the tunica albuginea, and adhesion of the skin. The superficial veins are generally enlarged. Metastasis occurs early, and especially to the inguinal and retroperitoneal lymph-glands; in rare instances, to the supra-clavicular lymph-glands. The tumors are usually soft, medullary, or encephaloid carcinomas. On section, the surface is opaque, whitish, and often marked with hemorrhagic areas; cancer-juice can be expressed. Sometimes the surface is glistening and homogeneous, and there is no juice. Mucoid and fatty degeneration is common. Islands of cartilage are often present—chondrocarcinoma—together with striped muscle-cells; and even combinations of carcinoma with sarcoma have been described. Such mixed tumors belong to the group of sarcomas, and can be explained only upon the theory of embryologic misplacement.

Cysts result from retention of secretion in the tubules or in vestiges of embryologic structures, as, of the Wolffian body, Müller's duct (hydatids of Morgagni), or the paradidymis, or organ of Giraldès. The cysts may be filled with a clear or a milky fluid (galactoceles), and sometimes contain spermatozoa (spermatocele). Cysts are frequent in tumors.

Teratoma.—Many tumors of the testicle are teratomas in that they are mixtures of various types of tissue, which may or may not be normally present in the organ. They are congenital, but often do not begin to grow until puberty.

Wilms (*Ziegler's Beiträge*, xix., 233) considers that they spring from all the three layers of the embryo. The tumors, as a rule, are benign, but may become, clinically, at least, malignant. They are not comparable to the mixed tumors of the parotid, as the latter are not derived from all the embryonic layers. Wilms proposes the name *embryoid tumors* for them.

Dermoid cysts are rare. They have been looked upon as rudimentary parasites or fetuses resulting from parthenogenesis, it being held that the female element supposed to be present in the spermatozoon becomes impregnated.

Among **parasites**, the echinococcus occasionally occurs in the epididymis and testicle, or in the cavity of the tunica vaginalis.

Hydrocele.—Hydrocele is an accumulation of fluid in the tunica vaginalis of the testis or of the spermatic cord. Hydrocele of the testicular tunica vaginalis is nearly always inflammatory in origin. It may be acute or chronic. The acute is usually associated with gonorrhea; less often with other inflammations or with injuries. The fluid is generally clear and serous, but may contain blood, leukocytes, and fibrinous flocculi. *Chronic hydrocele* is either a sequel of the acute or begins insidiously. Sometimes it is due to pressure upon the spermatic veins. The amount of fluid varies; it may reach enormous proportions. It is, as a rule, clear, straw-colored, and has a specific gravity of about 1022; its reaction is slightly alkaline. Cholesterin crystals may be present. Sometimes the fluid contains blood.

In long-standing cases the serous surface is opaque, the wall thickened, and occasionally infiltrated with deposits of lime salts. Sometimes fungoid excrescences form (periorchitis proliferata), the detachment of which gives rise to the presence of free bodies in the sac. Bands of adhesions may also develop between the layers—periorchitis adhæsiva. Multilocular hydrocele may be due to such bands of adhesions dividing the sac into chambers, or to congenital malformation of the tunic. The testicle usually suffers very little change.

Hydrocele of the cord consists of an accumulation of fluid in the unobliterated funicular process of the tunica vaginalis. When occurring independently of testicular hydrocele, it is termed encysted hydrocele.

Hematocoele.—An acute hydrocele may be converted into a hematocoele by the admixture of blood. Primary hematocoele may be produced by injuries, especially contusions of the testicle; also by the hemorrhagic diathesis. Hematocoele of the cord needs no separate description.

SEMINAL VESICLES AND VAS DEFERENS.

The seminal vesicles may be absent on one or both sides, or they may be fused. The ejaculatory ducts may be abnormal in number and position.

Inflammation of the seminal vesicles—spermatocystitis or vesiculitis—and of the vas deferens—deferentitis—is usually due to extension of inflammation from the epididymis, and is generally gonorrheal in origin. The seminal vesicles are swollen; epididymitis may be, but is not always, present. The microscopic appearances, according to Collan,¹ are as follows: The cavity is filled with round cells, principally mononuclear in type, detached epithelium, and globulin particles. Spermatozoa are usually present, unless there has been a closure of the seminal duct through epididymitis. In advanced cases the inflammation penetrates deeply into the submucous tissue, and causes destruction of the epithelium and scar formation, the vesicles being converted into fibroid cirrhotic bodies.

Tuberculosis generally accompanies urogenital tuberculosis; occasionally it appears to be primary. The vesicles are enlarged, and the walls thickened, firm, and caseous.

Tumors.—Primary carcinoma and sarcoma are very rare. They may appear secondarily, however, by extension from the neighboring structures, as the rectum. Cysts are usually the result of obstruction of the ejaculatory ducts. Calculi are sometimes found, especially in case of obstruction of the ducts. They have a nucleus of spermatozoa, epithelium, and mucus, and are usually small and white.

THE PROSTATE.

Absence of the prostate is rare, and usually accompanies other grave malformations of the genital tract. Hypoplasia, or congenital smallness, has been noted. Englisch² states that there is occasionally a congenital hypertrophy in children. Atrophy occurs in wasting diseases, from the pressure of tumors of neighboring parts, and not rarely in old age. Hypertrophy will be discussed later.

Prostatitis.—The causes of inflammation of the prostate are gon-

¹ *Ueber Spermatocystitis gonorrhoeica*, 1898.

² *Jahrbuch f. Kinderheilk.*, viii., 1875, 60.

orrhœa, injury to the prostatic urethra by instruments, irritant applications, and the passage of stones. External trauma and exposure to cold are doubtful causes. Some have held that the bicycle is responsible for inflammation of the prostate, but Thompson, White and Martin, and Guyon deny this. Sexual excesses, constipation, and diseases of the rectum, by causing congestion of the prostate, predispose to inflammation. Prostatitis also occurs in infectious diseases—typhoid fever, small-pox, pyemia, and glanders. Among bacteriologic agents, the pyogenic cocci, the gonococcus, and the *Bacillus coli communis* have been found. Prostatitis may be either acute or chronic. The acute may be subdivided into catarrhal, follicular, and suppurative, or parenchymatous.

Catarrhal prostatitis is, as a rule, observed only clinically.

Follicular Prostatitis.—As in follicular tonsillitis, there is an obstruction of the follicles, with the formation of small sacs containing desquamated epithelium, leukocytes, and detritus. Suppuration of the gland may ensue.

Suppurative Prostatitis (also called *Parenchymatous Prostatitis*).—This is characterized either by the formation of small abscesses or by a diffuse phlegmonous inflammation, with, at times, complete destruction of the gland-tissue. Abscesses, both small and large, often pass unnoticed. They may extend to the periprostatic tissues—suppurative periprostatitis—in which case thrombosis of the veins of the prostatic plexus is likely to take place. Softening of the thrombi not rarely gives rise to septic embolism and general pyemia. Perhaps it is also the cause of gonorrheal endocarditis. In all cases of cryptogenic pyemia, search should be made for prostatic abscesses. The abscesses may rupture into the urethra. Suppuration may end in fibrosis of the prostate, with gradual atrophy.

Chronic prostatitis may follow the acute or may come on insidiously. The principal cause is gonorrhœa. There is a discharge of a more or less viscid secretion (prostatorrhœa), containing desquamated epithelium, leukocytes, and amylaceous bodies, Böttcher's crystals, and peculiar casts resembling renal tube-casts. The prostate may be reduced in size or enlarged, and is either soft and of a dirty-brown color, or fibroid and glistening. Microscopically, the lumen of the tubules is filled with desquamated epithelium, leukocytes, and amylaceous bodies. About the glands are leukocytes and newly formed spindle cells. Cicatricial bands pass in all directions; their contraction may occlude the ejaculatory ducts; sometimes, however, it tends to keep them patulous, this constituting one cause of spermatorrhœa.

Tuberculosis.—Tuberculosis of the prostate is most frequent in young adults, and is generally a part of a urogenital tuberculosis; but it may be primary in the organ, from hematogenic infection. The gland is enlarged, and is usually the seat of extensive caseous change; more rarely, of typical miliary tubercles. The caseous sacs may rupture into the rectum, urethra, or bladder. In rare instances a general miliary tuberculosis is produced.

Hypertrophy of the Prostate.—The normal prostate varies in size and weight with the age, but even for the same age is subject to wide individual variations. It is small in children, and reaches its maximal growth at the height of the sexual life, at about the fortieth year. It then measures 4 cm. in length, 4 to 4½ cm. in width, and 2 to 2½ cm. in thickness, and weighs from 16 to 17 grams. In advanced life it often undergoes a peculiar pathologic change that causes an enlargement. The frequency of

this hypertrophy of the prostate is differently stated by different authors. It is probably present in one out of three men past the age of sixty. It may, however, occur much earlier in life. In extreme old age it is rare.

Etiology.—The etiology of enlargement of the prostate has been a subject of much speculation. The principal theories advanced in its explanation are the following :

(a) That the enlargement is analogous to fibroid tumors of the uterus—a theory based upon a belief in a homology between the prostate and the uterus. But the prostate and the uterus are not homologous ; the homo-

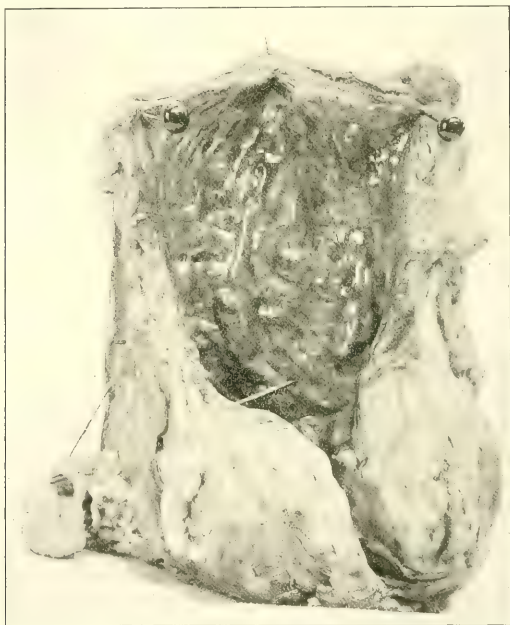


FIG. 326.—Enlarged prostate.

logue of the latter is the prostatic utricle, which, however, has nothing to do with enlargement of the prostate.

(b) That the enlargement is part of a general arteriosclerotic process. While hypertrophy of the prostate and arteriosclerosis are frequently associated, there is no connection between the two, and they often occur independently.

(c) That the enlargement is compensatory for weakness of the bladder, the enlarged prostate acting as a sort of buttress. This cannot be correct because the prostate is purely sexual in function, and has nothing to do with micturition.

(d) That the enlargement is the result of inflammatory processes, brought

about by overstimulation during the period of sexual life. In answer to this it may be said that the enlargement has not the characteristics of an inflammatory hyperplasia.

It will be seen that there is no single theory that satisfactorily accounts for hypertrophy of the prostate. There is some connection between the process and the testicles, and it is probable that some alteration in the function of the latter is responsible for enlargement of the gland in old age. Moreover, removal of the testicles causes prompt atrophy of the enlarged organ.

Various local conditions, such as hemorrhoids, instrumentation, gonorrhea, constipation, and sexual excesses, are supposed to play a part in the

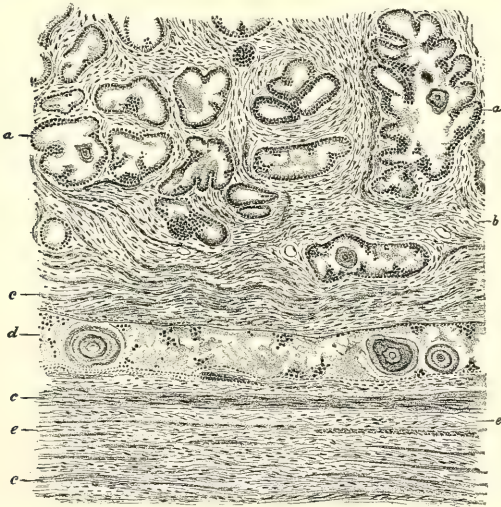


FIG. 327.—Hypertrophy of the prostate (adenomatous form): *a*, acini, in part dilated and containing small amylaceous bodies; *b*, interacinous connective tissue; *c*, bundles of non-striated muscle; *d*, gland-duct containing large lamellated amylaceous bodies; *e*, intermuscular connective tissue (Weichselbaum).

production of hypertrophy of the prostate. Their influence, however, is slight.

Effects.—The first effect is obstruction to the exit of urine. The bladder becomes hypertrophied and dilated, and its wall ribbed (trabeculated bladder). Cystitis may develop; also dilatation of the ureters and pelvis of the kidney. The prostatic veins become dilated, and the ejaculatory ducts obstructed.

Pathologic Anatomy.—The enlarged prostate weighs from 23 to 85 grams (the largest known attained a weight of 288 grams). The enlargement may involve one or both of the lateral lobes, or the posterior isthmus—the so-called median lobe (Home's lobe, lobus pathologicus)—or all three may be enlarged together. As a rule, the enlargement produces a characteristic change in the shape and width of the posterior urethra. The median

lobe often projects as a rounded hemispheric tumor into the lumen, causing obstruction. Occasionally valve-like folds are produced in the mucous membrane by the enlargement. On section the gland is firm, whitish, and dotted with brownish points—the so-called “grains of snuff.” Frequently there is a bulging of rounded masses, which can be readily shelled out.

Pathologic Histology.—The enlargement involves all elements—the glandular, muscular, and connective tissues, but generally in varying proportions, so that it is possible, according to Casper, to recognize three forms—the nodular myomatous, the diffuse fibromyomatous, and the adenoid hypertrophic. Mansell Moullin¹ believes that all enlargements of the prostate begin in the growth of imperfectly formed gland tubules. Others consider that the primary change is an overgrowth of the stroma. In typical cases the section shows an abundance of stroma of muscular and connective-tissue cells, with atrophy of the glands, the tubules having a low epithelial lining and a dilated lumen, in which detached epithelial cells, detritus, and amylaceous bodies are found. In some cases or in certain areas the glandular hyperplasia may be so marked as to suggest adenoma; in others again, nonstriped muscular tissue predominates, the masses resembling liomyoma of the uterus.

Castration produces atrophy of the prostate, especially of the glandular elements. The atrophy begins within a few days after the operation. The same result, although in a less marked degree, is produced by a division of the vas deferens (vasectomy). Floderus² states that the atrophy is chiefly due to a reduction in the blood and lymph content of the gland. Lesin³ found atrophy of the glandular and muscular elements and the development of fibrous tissue. In dogs the first change occurs, in forty-eight hours, in the epithelial cells, and consists in the appearance of fat droplets.

Cowper's Glands.—Inflammation of these glands (cowperitis) may accompany gonorrheal urethritis. Not rarely it leads to suppuration and to the formation of sinuses. Obstruction of the ducts is followed by cystic dilatation. Carcinoma of the glands has also been described.

Carcinoma.—Carcinoma is rare, and often overlooked, not alone during life, but even at autopsy. It occurs especially in advanced age, but may be observed in youth. Prostatic carcinoma has a marked tendency to metastasis, and the extent of the secondary growths, as in the case of thyroid carcinoma, is out of proportion to the size of the primary tumor. Metastasis occurs early to the inguinal lymph-glands; also to the retroperitoneal and pelvic glands, and to those along the aorta and vertebræ. Sometimes the supraclavicular glands are involved. A peculiar feature of prostatic carcinoma is the frequency of metastasis to the bony skeleton, the secondary growths being characterized by the formation of osseous tissue.⁴ Such prostatic growths have been called osteoplastic carcinomas. The enlargement of the prostate may be uniform or may affect only one lobe. The appearance is sometimes that of simple hypertrophy. On section, the surface is interspersed with nodular masses; but there may be large, well-defined tumors. Occasionally the surface of section is suggestive of tuberculosis, as in a case reported by Engelhardt.⁵ Carcinoma may be engrafted upon antecedent hypertrophy. The carcinomatous growth is of the nature of adenocarcinoma.

Sarcoma.—Sarcoma of the prostate is rare. It may be of the round-

¹ *Enlargement of the Prostate*, 1894, 18.

² *Nord. med. Arkiv*, 1897, No. 24.

³ *Inaug. Diss.*, Moscow, 1897.

⁴ Cone, *Johns Hopkins Hosp. Bull.*, 1898; Bamberger and Paltauf, *Wien. klin. Wochenschr.*, 1100, 1899.

⁵ *Virchow's Archiv*, clviii., 568.

cell or spindle-cell type. It often spreads locally, but does not involve the lymph-glands, as a rule. Metastasis may occur to the lungs and liver, and in rare cases, as in carcinoma, to the bones.

Cysts.—Cysts are due to obstruction of the ducts of the glands or to dilatation of rests of the Müllerian ducts. Echinococcus cysts are rare.

Concrements and Stones.—In nearly all prostates, but especially those of advanced life, peculiar, concentrically striated bodies are found, which stain red with gentian- or methyl-violet, and mahogany-brown with iodine. They have usually been considered amyloid—corpora amylacea; but according to Posner they consist of an albuminous substance, impregnated, to a greater or less extent, with lecithin. On naked-eye examination they look like grains of snuff dotted over the surface of the gland. They may coalesce, and, by incrustation with lime salts, may be transformed into calculi. Such calculi at times lead to chronic inflammation and atrophy of the gland.

SPERMATIC CORD.

Diseases of the spermatic cord are rare. **Inflammation**—funiculitis—may be due to extension from posterior urethritis or to traumatism. Of **tumors**, lipoma and sarcoma have been described. The former is often very large. **Cysts** of the cord are either true seminal cysts developed from remains of the Wolffian body or encysted hydroceles resulting from dilatation of a patulous funicular process of the tunica vaginalis. Some of the congenital cysts are filled with mucoid or tallow-like contents. **Varicocele** is a dilated and tortuous condition of the veins of the spermatic cord. It is most common between the ages of fifteen and twenty-five, and affects especially the left side, because the left spermatic vein does not empty directly into the vena cava, but at right angles into the renal vein, and also because it runs up behind the rectum.

PENIS AND SCROTUM.

Fractures.—So-called fracture of the penis consists in rupture of the fibrous sheath of the cavernous bodies while the organ is in a state of erection. It is brought about by traumatism, and occurs most readily when the sheath of the corpora cavernosa is calcified. The seat of fracture may be behind the glans, in the middle, or at the root of the penis. Extensive and even fatal hemorrhage may result. In many cases the urethra is ruptured. *Dislocation* of the penis is usually due to external violence.

Senile Changes.—These, which have been especially studied by Schurigin,¹ consist of sclerosis of the vessels, atrophy of the nerves and of the touch-corpuscles, thinning of the walls of the cavernous bodies, and atrophy of the nonstriated muscle-fibers.

Inflammation.—Inflammation may affect the cavernous bodies (cavernitis or penitis), but is more frequent in the glans (balanitis) and in the lining of the foreskin (posthitis). **Balanoposthitis** is due to irritation by retained secretions, especially when the foreskin is too long; also to chancre and chancreoid. The parts are swollen, edematous, and red. The foreskin may be so swollen that it cannot be retracted (*phimosis*); if the swelling occurred while the prepuce was retracted, the latter cannot be brought for-

¹ *Vratsch*, li., 1897.

ward (*paraphimosis*). If these conditions are not relieved, they may lead to gangrene. **Cavernitis**, or **penitis**, is chiefly due to injuries and to gonorrhea. It may also be brought about by erysipelas, small-pox, typhoid fever, etc. Chronic cavernitis leads to the formation of cartilaginous or bony masses in the sheath of the cavernous bodies.

Tuberculosis is usually due to direct infection, as, *e. g.*, after ritual circumcision.¹ Whether it can be brought about by coitus in cases of tuberculosis of the female genitalia has not been definitely established. The disease takes the form of tuberculous ulcers, which sometimes resemble carcinoma. In rare instances the glans is involved by extension from the urethra.

Syphilis.—The glans and prepuce are the most common seats of the initial sclerosis or chancre. It is particularly at the corona and the frenum that this lesion occurs. The secondary lesions, in the form of the condyloma latum, and tertiary lesions, *viz.*, the gumma, also occur. The microscopic features of these have already been described.

Chancroid or **soft chancre** is a specific lesion brought about through infection during coitus. It produces rounded, "punched-out" ulcers, covered with a whitish slough. It is generally multiple, and is auto-inoculable. Sometimes the ulcers become phagedenic and cause extensive destruction. Ducrey has discovered in chancroidal lesions a short bacillus with rounded ends, often occurring in chains between the cells; the specific nature of this, however, has not been definitely proved.

Tumors.—**Elephantiasis** of the penis and scrotum is in reality not a true tumor. It may be due to the *Filaria sanguinis hominis* or to chronic inflammation, or it may follow disease or extirpation of the inguinal glands. Elephantiasis of the scrotum—lymph-scrotum—may be associated with a similar condition of the legs.

Condyloma acuminatum is a moist, pointed excrescence on the foreskin. It is often multiple, producing large, cauliflower-like masses. Being due to irritation of the prepuce, it is not, in a strict sense, a tumor. It consists in a branching proliferation of the papillary layer of the skin, and is covered with a thick stratum of squamous epithelium. Both macroscopically and microscopically it often resembles squamous epithelioma; but the regularity of the epithelial covering, the nonpenetration of the epithelium into the connective tissue, and the movability of the growth over the underlying skin, serve to distinguish it from carcinoma.

Cornu cutaneum is a localized horny growth found on the glans and scrotum. It may be associated with squamous carcinoma. Occasionally there is a diffuse thickening of the horny layer of the glans (keratosis).

Chondroma and **osteoma** are sometimes found in the cavernous bodies. As regards osteoma, it is probably due to chronic irritation of the fibrous sheath.

Lipoma, **angioma**, and **sarcoma** occur, but are rare.

Carcinoma is most frequent at the attachment of the prepuce to the glans, and usually has a papillomatous character. Extensive cauliflower-like masses form and surround the penis to a greater or less extent. In rare cases the growth produces merely a flat, infiltrating ulcer. Histologically, both forms are squamous carcinomas with extensive horny change, the formation of epithelial pearls, and marked inflammation of the stroma.

¹ Malécot, *Ann. des Mal. des Organes génito-urinaires*, 1893, xi., 838.

Metastasis occurs primarily to the inguinal glands, but, according to some writers, the pelvic glands are first affected. General dissemination is uncommon. In a number of cases penile carcinoma has developed as a sequence of sexual intercourse with women having carcinoma of the cervix, and the possibility of direct transmission of the disease suggests itself.

Carcinoma of the scrotum is interesting in that it seems to occur by preference in persons following certain occupations: thus, among chimney-sweeps and among paraffin and tar workers.

Cysts.—Dermoid cysts are not rare in the scrotum. They often have a complicated structure (fœtus in fœtu).

Preputial Stones.—Small concretions resulting from incrustation of desquamated epidermis and smegma with urates and phosphates are sometimes formed under the foreskin. Occasionally they attain a large size.

THE FEMALE GENITAL TRACT.

THE VULVA.

Malformations.—Complete Absence of the Vulva (*Atresia of the Vulva*).—Very rarely there occurs a complete failure in the development of the urogenital sinus. Such a condition has been found only in nonviable fetuses, as acephalic monsters and siren deformities, and is always associated with marked deformities of the internal genital organs. The skin is seen stretched evenly and unbroken from the pubes to the coccyx. An arrest in the development of the urogenital sinus may take place, which results in a persistence of the condition which existed in a stage of embryonal development; thus there may be epispadias, hypospadias, a persistent opening of the bowel into the vestibule above the hymen (*anus præternaturalis vestibularis*), with or without a patent anus in the normal situation. Also a congenital retroperitoneal fistula and various malformations of the perineum, labia majora, and labia minora are described.

A condition of abnormal conglutination of the inner surfaces of the labia minora above and the labia majora below not rarely occurs. This is usually found in young children, and is believed by some authorities to be an inflammatory cohesion.

The vulva may be **undeveloped** (*vulva infantilis*) where the normal changes at puberty fail. The external genitals appear more or less like those of a child—the pubes poorly developed and free from hair, the vestibule shallow, and the labia majora and minora small and flat. The uterus is, as a rule, also undeveloped.

An **increase in the number of labia minora** has been described as a congenital deformity, resulting from a splitting of the genital clefts from which the labia minora are formed.

Hyperplastic changes in the external genitals are probably congenital, or at least the result of congenital tissue-change. An excessive development of the labia minora and prepuce of the clitoris (10 to 26 cm. in length) is seen in certain races, as the Hottentot, and also occasionally in the Caucasian woman. It is known as the *Hottentot apron*. The clitoris may be found the size of a penis in some savage races and, rarely, in prostitutes. It is also frequently hypertrophied in hypospadias. The labia majora in a few instances have been seen overdeveloped, but this is probably always due to new growths, as lipoma and elephantiasis (Nagel).

Hernia through the inguinal canal may present in the labium majus (*hernia inguinalis labialis*). A hernia may also extend from beneath the ramus of the pubes and present in the inferior portion of the labium majus (*hernia labialis inferior*).

Circulatory Changes.—A condition of venous stasis in the external genitals very frequently occurs where there exists a pathologic or physiologic tumor in the pelvis, or with any venous stasis of the lower half of the

body. The veins are filled and dilated, often causing the formation of a tumor of veins (varicose veins) which may reach the size of two fists. There is often associated edema. The veins of the labia majora are usually most involved. Subcutaneous rupture of one of these veins may take place during parturition, or from traumatism, producing a hematoma. That resulting from parturition sometimes reaches a very large size. Thrombi may form in the dilated veins, and, through calcification of these, phleboliths. Polypoid angiomas of the mucous membrane of the vestibule, composed of dilated vessels in a connective-tissue stroma infiltrated with blood, are quite common. Edema is found in inflammation of the vulvar and neighboring tissues, as the pelvic bones or cellular tissue. It is also often associated with nephritis and heart disease.

Inflammations of the vulva are commonly those which affect the skin in other portions of the body, the tissues external to the vestibule having many of the characteristics of the skin. Thus there may be a diffuse erythema, eczema, herpes progenitalis, prurigo, impetigo herpetiformis, acne, furunculosis, gangrene, and erysipelas. A frequent and most intense form of erythema is due to infection with the gonococcus. This inflammation is mostly observed in children, but may occur during adult life. Gonorrhea is here of short duration, except where the glands of Bartholin are involved. The labia minora, the glans and frenum of the clitoris are seen edematous and covered with pus, and here and there are patches covered by necrotic epithelial cells and leukocytes, under which is an area of erosion. The hymen ring is swollen and its edges eroded. The microscopic changes are identical with those seen in other surfaces covered with squamous epithelial cells—the vagina and vaginal cervix. Frequently the small glands of the vulva are infected—follicular vulvitis. The gland openings are reddened and abscesses often form. The disease persists for weeks and months.

Acute gonorrheal vulvovaginitis occurs in the newborn, the infection taking place directly from the mother during labor or indirectly through washes, etc. Organic adhesion of the labia majora and minora may follow. Vulvitis may be produced by the *Saccharomyces albicans*.

Catarrhal inflammation of the internal genitals, carcinoma of the cervix, etc., from which irritating discharges flow over the vulva; uncleanness, irritation from walking, and the like, often cause more or less severe inflammation; the vulva becomes swollen, reddened, and not rarely excoriations appear on the labia.

Phlegmonous vulvitis, a diffuse inflammation of the cutis and subcutaneous tissue, may follow injury during parturition.

Diphtheric inflammations, pseudomembrane formation, and ulcers may occur in diphtheria and puerperal sepsis, croupous inflammation in puerperal sepsis, measles, typhoid fever, scarlet fever, and cholera, extending either from the intestine, vagina, or uterus. This inflammation may terminate in gangrene. Gangrene may also result from chancroid, phagedenic ulcer, or severe disturbance of the circulation, injury during parturition, venous thrombosis, hemorrhage, etc.

Kraurosis vulvæ, a rare disease first described by Breisky, is, so far as is known, a chronic inflammatory hyperplasia of the connective tissue, with a tendency to cicatricial contraction, inflammatory edema of the upper layers of the corium and epidermis, and degeneration of the elastic tissue. The disease involves the mucous membrane of the vestibule, vagina, labia

minora, the frenum and prepuce of the clitoris, and inner surfaces of the labia majora. Its etiology is unknown. The skin of the vulva appears stretched, smooth, glistening, and dry, often torn or fissured. The normal sulci disappear, the labia minora become stenosed, and the vagina is often constricted. The kraurotic parts are a dull-gray color, and where contraction has taken place a brownish red. The condition is believed to be a diffuse connective-tissue hypertrophy, belonging to the same class of diseases as scleroderma and elephantiasis Arabum.

Chancroid and its complications are most frequently found along the margins of the labia majora and minora, about the fourchet and urinary meatus.

Syphilis of the vulva appears in the form of any of the characteristic lesions of this disease—chancre, mucous patch, condylomata latum, secondary syphilids, and very rarely gummas and gummatous infiltrations. The tertiary lesions may spread, producing extensive warty growths of the skin, which resemble elephantiasis. Phagedena may develop, with extensive destruction of tissue and resultant cicatricial deformity.

There has been described as *ulcus rodens vulvæ*, lupus, chronic elephantiac ulcer, a circumscribed chronic inflammatory hyperplasia or ulcer of the vulva, the etiology of which has not been determined. The disease disappears, reappears, progresses, and persists for years. The microscopic changes, aside from those of simple inflammation, are not characteristic of any special disease. It is thought by some authorities to be lupus, by others to be a syphilitic lesion, and by Koch that it is caused by lymph-stasis and follows destruction of the inguinal glands.

Tuberculosis of the vulva is extremely rare, and is probably always secondary to a tuberculous process in other portions of the body, as the vagina, rectum, cervix uteri, endometrium, or from pulmonary tuberculosis. It appears as an ulcer with serrated edges and a ground of gray miliary nodules, or as a fistula, and it has been found as a tuberculous infection of a mucous polyp.

Noma appears in a similar manner to that of the mucous membrane of the mouth.

Tumors.—**Papillary growths** of the vulva occur mostly as the result of previous irritation, commonly gonorrhea—the pointed condylomata (condylomata acuminata), or venereal warts. Rarely warts appear which have no relation to precedent inflammation.

Elephantiasis develops from the labia majora, labia minora, or clitoris; rarely it has a multiple origin. The labium majus may be so enlarged that it reaches the knee. It appears partly in the form of a hard, lardaceous growth, and partly as a connective-tissue or gelatinous edema, through which the part is enlarged and loses its form. As a rule the surface is smooth (elephantiasis glabra), at other times covered with small nodules (elephantiasis tuberosa) or with small warty growths resembling the pointed condylomata (elephantiasis condylomatosa). Some cases appear as an inflammatory process, or as acquired lymph-stasis caused by disease of the lymph-glands and changes in the lymph-vessels. In other cases it is found as a hyperplastic growth at birth, or at least there is a congenital predisposition to its development. This form is known as pachydermatocele, or elephantiasis molluscum, or mollis.

A congenital lymphangiectasis, or cavernous cystic lymphangioma of the

labia majora, may sometimes occur. Elephantiasis may develop in the site of this lymphoid change.

Urethral caruncle, a mucous polyp, is frequently found at or near the urethral orifice. It varies in size from that of a small berry to that of a hazelnut, is soft, bright red in color, has a smooth or raspberry-like surface, and is usually pedunculated. Histologically it is composed of a loose connective-tissue stroma infiltrated with leukocytes. Also a few tubular glands are seen. The surface is covered with the squamous epithelium of



FIG. 328.—Fibroma arising in the connective-tissue of the right labium majus.

the vestibule, beneath a thinned portion of which there may be seen small round-cell infiltration.

Fibroid nodules or **polypi** occasionally grow from the connective tissue beneath the surface of the labia majora or minora, or rarely from the clitoris. They are composed of flabby, edematous connective tissue covered by normal skin. Sometimes mucous tissue is found, and the tumor is regarded as a myxoma or fibromyxoma. Injury and inflammation are thought to influence their growth.

Lipoma develops from the fat-tissue of the labia majora or mons veneris, and appears as a circumscribed tumor, rarely as a pedunculated tumor.

Carcinoma of the vulva appears either as a nodular or papillary tumor, a diffuse infiltration of the skin, or a deep, crater-like ulcer. It arises

chiefly from the skin of the labia majora, less often from the labia minora, and rarely from the clitoris, its prepuce, the anterior and posterior commissures, or in relation with the external urinary orifice. Histologically it is a squamous epithelioma, sometimes having an alveolar character. The tendency to epithelial pearl formation is absent. That which returns after excision is described by Gebhard as sometimes resembling lymphatic carcinoma. Of the female genital tract, the vulva is the second site of frequency of carcinoma. It commonly occurs between the ages of forty and fifty years. Metastatic carcinoma is here extremely rare.

Round- and spindle-cell **sarcoma** in a very few instances have been found developing in the tissues of the vulva. A myxosarcoma has been described; also a melanotic sarcoma and melanocarcinoma.

BARTHOLIN'S GLAND.

Inflammation of the duct of Bartholin's gland (Bartholinitis) is a very common sequel of gonorrhea. It is observed in adults, most frequently in prostitutes, rarely in children. The infection may take place in any stage of gonorrhea, and persist for months and even years after the primary infection. The ducts of both glands are, as a rule, infected. It appears as an acute or chronic inflammation of the duct, pseudo-abscess or true abscess of the duct, retention-cyst of the duct, fistula, or as an inflammation or abscess of the gland and duct. In the first instance the orifice of the duct is swollen, everted, and surrounded by a small area of redness (the gonorrheal macule), and the duct contains a small amount of pus. In about one-third of the cases closure of the duct occurs, and the duct becomes filled and dilated with purulent material to perhaps the size of a pigeon's egg, the wall and its epithelium remaining intact—pseudo-abscess (Jodassohn). A mixed infection of the duct with gonococci and pyogenic organisms (usually the *Staphylococcus pyogenes aureus*) causes a necrosis and destruction of the duct-wall and the formation of a true abscess. Where the retention of secretions and purulent material in the chronically inflamed duct occurs slowly and the gonococci have lost their virulence a retention-cyst is formed. These retention-cysts are filled with mucopurulent fluid sometimes containing gonococci and other organisms. Such cysts may form independently of a gonorrheal infection. These abscesses and cysts distend the posterior portion of the labia majora. After rupture of an abscess or cyst a persistent fistula remains. In the mixed gonorrheal and staphylococcus infection the inflammation occasionally extends to the gland itself.

Alveolar carcinoma rarely originates in the glandular epithelium. An adenoma also has been described.

THE HYMEN.

The hymen is normally a delicate annular membrane with a central perforation which is most often crescentic in shape (hymen semilunaris), with the edges smooth, or less frequently dentated or fringed (hymen denticularis or fimbriatus). There may be two symmetric openings side by side, numerous punctate openings (hymen cribriformis), an exceedingly small opening, or the membrane may be imperforate (atresia vaginæ hymenalis). There may be a second hymen in front of the normal one, or side by side where there are two vaginas. Rarely it may be entirely absent, or more

often represented only by a few ill-developed fibers. It may be irregularly carved out of thickened tissue (sculptured hymen). It has been observed hypertrophied, projecting 1 to 3 centimeters (Scanzoni).

Cysts, about 1 millimeter in diameter, are found in the vestibule surface or in the free edges of the hymen. They are probably retention-cysts.

THE VAGINA.

Congenital Deformities.—**Complete absence** and **complete atresia** of the vagina occur with the same failures of development in the uterus, resulting respectively from agenesis and atresia of the Müllerian ducts. In the first only a solid connective-tissue cord occupies the position of the vagina. In the second there is an extremely rudimentary vagina, the atresia extending its entire length. *Partial atresia* is found as a membranous occlusion of the lower portion of the canal. After puberty, with the beginning of menstruation, blood collects in and distends the vagina above such an atresia (hematokolpos); also, finally, the cervix and uterus may be distended (hematometra), and even the Fallopian tube (hematosalpinx). The blood thus retained is peculiar in that it is never clotted, but is a more or less homogeneous, chocolate-colored mass. Decomposition and bacterial infection of this retained blood may occur, with vaginitis and the formation of a pyokolpos, the infection probably taking place through the rectovaginal wall.

Congenital stenosis, through arrest in development, may occur, the stenosis being diffuse or localized; also transverse bands are sometimes found. In the more extensive stenosis a similar defect is found in the uterus. If the uterus is infantile, the vagina also remains short and narrow (*vagina infantilis*).

A *congenital cohesion* of the vaginal walls occurs, extending even throughout its entire length.

From a failure of union in the median line of the distal ends of the Müllerian ducts there results a **complete** or **partial longitudinal septum** in the vagina. Where there is a complete septum, a right and a left vagina are formed. The partial septum is usually found in the upper third of the vagina. A double vagina is present with uterus didelphys, uterus duplex, and uterus septus.

Acquired Deformities and Injuries.—Traumatic separation of the muscular, fascial, and connective-tissue supports of the vagina and pelvic floor are usually followed by more or less prolapse and eversion of the lower portion of the posterior, and often the anterior vaginal wall through the vaginal ostium. Also in this deformity there is commonly an associated and equal degree of prolapse of the anterior wall of the rectum into the vagina (rectocele) and the posterior wall of the bladder (cystocele). Rarely a rectocele is caused by a dilatation of the anterior wall of the rectum without injury to the vaginal supports, and a cystocele by dilatation of the posterior wall of the bladder. A slight prolapse of the anterior vaginal wall may result from dilatation of the urethra (urethrocele). The cul-de-sac of Douglas may be extended, separating the rectum from the posterior vaginal wall even to the vaginal ostium by the descent of intestine (posterior enterocele); likewise the vesico-uterine space may be deepened, the bladder being separated from the anterior vaginal wall (anterior enterocele). Such a

hernia-sac prolapses and everts the vaginal walls as in cystocele and rectocele. A similar separation of the rectum from the vagina and prolapse of the vagina are sometimes caused by the pressure of ovarian and uterine tumors or fluid in Douglas's cul-de-sac.

In partial prolapse of the uterus the upper portion of the vagina is inverted and prolapsed. In complete prolapse of the uterus it is completely inverted and prolapsed.

Injuries of the vaginal walls commonly result from parturition, and are lacerations and contusions. A slight laceration in the median line of the posterior vaginal wall at the vaginal ostium is very common, lacerations in the posterior vaginal sulci involving the levator ani muscle and pelvic fascia are very frequent, and not rarely a laceration in the median line of the posterior wall is extensive, extending through the perineum, sphincter ani muscle, and more or less up to the rectovaginal wall, even to as high as the uterus. Lacerations in the anterior vaginal wall near the urethra, the lateral walls, and at the vaginal vault are rarely observed. In a few instances more or less extensive lacerations at the vaginal vault have been caused by violent sexual intercourse where there was a disproportion between the male organ and the vagina.

Contusion of the vaginal walls may be so severe that more or less necrosis of tissue results, often with the formation of communications or fistulas between the vagina and bladder (vesicovaginal fistula), vagina and rectum (rectovaginal fistula), vagina and urethra (urethrovaginal fistula), and vagina, bladder, and urethra (urethrovesicovaginal fistula). Such fistulas may also result from operative or other forms of traumatism and disease (obstetric forceps, pessaries, and lacerations, carcinoma, and syphilis). The size of the fistulous opening varies from that scarcely to be detected up to a wide destruction of one wall. The edges are sharp and thick, or thickened and covered with phosphatic deposit. Contusions or abrasions may cause atresia, or even partial or complete obliteration of the vagina. Hematomata occasionally develop in the vaginal walls as on the vulva.

Inflammation of the Vagina.—Inflammation (vaginitis, kolpitis) of the vaginal mucous membrane is commonly of bacterial origin, but may arise from mechanical, chemical, or thermal irritations. The actual influence of bacteria in the production of the anatomic changes is not well understood, nor can a pathologic lesion be determined to be caused by the infection of a special pathogenic bacteria, except in the very rare cases of true gonorrheal, diphtheritic, and perhaps emphysematous vaginitis. The vagina, as compared with other mucous membranes, is very resisting to inflammation, the squamous epithelial portion of the mucosa forming a strong barrier to bacterial infection. Also such infections are further resisted by the bactericidal action of the normal vaginal secretions; its acid reaction, the antagonizing power of the vaginal bacilli of Döderlein, and the presence of phagocytes.

Inflammation of the vagina is to be classified from its anatomic and clinical forms as follows:

Catarrhal vaginitis appears as an acute and chronic inflammation. Its clinical cause is commonly the stagnation of purulent, irritating discharges in the vagina; mostly a gonorrheal discharge from the cervix uteri. Sometimes it is induced by mechanical, chemical, or thermal irritations, and it

may occur during the course of the infectious fevers, as measles, scarlet fever, small-pox, etc.

Acute Catarrhal Vaginitis.—The vaginal surfaces are seen diffusely reddened; the tissue is softened and often swollen. The vaginal secretion is increased in amount; it is a thin white or thicker yellowish-green fluid composed of desquamated epithelial cells, an abnormal number of leukocytes, and often specific pathogenic micro-organisms. The acidity is destroyed and the Döderlein bacilli decreased in number or absent. It is observed mostly in children, frequently as a vulvovaginitis. Histologically the squamous epithelial covering and the immediately underlying connective tissue are diffusely infiltrated with small round cells. The redness is caused by capillary injection and thinning of the epithelium from desquamation.

Chronic catarrhal vaginitis appears as a diffuse, evenly distributed inflammation and as an inflammation localized to the papillary bodies. In the former the vaginal surfaces are slightly reddened. The squamous epithelial covering and the immediately underlying connective tissue are, as in the acute inflammation, diffusely infiltrated with small round cells. In the latter bright-red papillary prominences are seen more or less diffusely spread over the vaginal surfaces, causing a granular appearance (granular catarrhal vaginitis). The round-cell infiltration and hyperemia are here localized to and form the papillary prominences. The epithelial covering of the prominences has frequently disappeared, forming minute erosions. The vaginal secretion does not distinctly differ from that above described.

Gonorrheal Vaginitis.—A true gonorrheal infection of the vaginal mucous membrane has rarely been observed in young children and in elderly and ill-developed women, the squamous epithelial covering of the vagina being atrophied, incompletely or poorly developed, and thus less resisting to the infection of the gonococcus. The gonococci are seen in leukocytes, in groups, or isolated between the squamous epithelial cells, and mostly in the underlying connective tissue. Otherwise the disease resembles the acute catarrhal inflammation.

Persistent chronic vaginitis, particularly that of gonorrheal origin, may result in a diffuse or localized papillary and connective-tissue hyperplasia, with finally contraction and narrowing of the vaginal lumen.

Senile vaginitis is an inflammation resulting from the infection of portions of the atrophic senile mucous membrane which has lost its epithelium. The lesions are reddened patches or ulcers of varying size, sometimes presenting the character of ecchymoses. Adhesions may form between such patches (adhesive vaginitis).

Croupous vaginitis rarely complicates a catarrhal vaginitis, the surface being covered with a gray pseudomembrane composed of fibrin and leukocytes. It is usually associated with a croupous enteritis.

Gummatous vaginitis (kolpitis gummosa) is characterized by the presence of a grayish-white covering to the entire vaginal surface, which separates, is thrown off as a cast of the vagina, and re-forms (Winckel). It is a separation of the epithelial layer of the vaginal mucous membrane (Birch-Hirschfeld). Its cause is not determined, but it is thought to be due to syphilis.

Empysematous Vaginitis (*Kolpohyperplasia Cystica*).—Occasionally during pregnancy, less often in the puerperium, the vaginal mucous membrane is found infiltrated with multiple small cysts containing gas. Other-

wise the vaginal surfaces appear normal. Histologically the subepithelial connective tissue is found thickly infiltrated with cystic spaces lined with epithelium or endothelium, probably dilated lymph-vessels. The surrounding connective tissue is infiltrated with small round cells and contains many large giant cells. The disease is no doubt due to a gas-forming micro-organism, but this organism has not been positively isolated.

Aphthous Vaginitis.—White raised patches on a reddened vaginal wall are sometimes found. They are caused by a vegetable parasite closely resembling the *Oidium albicans*.

Ulcerative Vaginitis.—From exposure and insult in prolapse of the vaginal wall, decomposition of secretions, pressure of foreign bodies, cauterization, etc., erosion, ulceration, and necrosis of the vaginal walls not infrequently take place. There may be sloughing and a destructive phlegmonous inflammation. Foreign bodies, as a pessary remaining in position for an indefinite length of time, may become buried in granulations and produce atresia; also they may perforate the vaginal wall.

Pseudomembrane formation may be found with puerperal infection, from decomposition of uterine carcinoma and polypi, with vesicovaginal fistula and intestinovaginal fistula. Also during the course of infectious fevers, as measles, small-pox, scarlet fever, typhoid fever, cholera, etc. With such pseudomembrane formation there is a diffuse swelling of the mucous membrane, and it is also deeply reddened. More or less cicatricial contraction and partial or complete obliteration of the vagina may follow.

Diphtheric ulceration, due to infection with the Löffler bacillus, has occasionally been observed. Also an erysipelatous vaginitis.

Ulcus Rodens Simplex.—Rarely a round ulcer having sharply defined nonindurated edges and a reddened ground is found usually on the posterior portion of the vaginal vault. It is believed to be caused by a blood-vessel change.

Ulcus Molle.—Under this name a small ulcer of the vagina resembling a chancreoid ulcer is described.

Paravaginitis and **perivaginitis** are rare inflammations of the submucosa or deeper connective, muscle, and elastic tissue of the vagina. The inflammation is localized or diffuse, and commonly progresses to suppuration. Its cause is injury by foreign bodies or during labor, followed by infection. A phlegmonous form has been described in which a great part or the whole of the submucosa is involved and becomes gangrenous. It is believed to be also caused by gonorrhea, typhoid fever, and, in the young, by other infectious fevers.

An abscess of Gärtner's duct extending into the vagina has been described (Kelly).

Syphilis is found in the form of an initial lesion, papule, or gummatose ulceration. Syphilis is localized here much more rarely than in the external genitals.

Chancroids of the vagina are very uncommon.

Tuberculosis is very rare, and appears as an ulcer or as miliary tubercles, extending from an advanced tuberculosis of the uterus, vulva, intestine, or possibly through the blood. One case of primary ulcerative tuberculosis has been described (Friedländer).

Tumors.—**Vaginal Cysts.**—Cystic formations in the vaginal wall beneath the squamous epithelial layer of the mucosa are not very infrequent.

They arise in the remains of or a persistent Wolffian or Müllerian duct (Gärtner's duct), which is found beneath the vaginal mucosa in the right or left anterior vaginal wall. Also they have developed from glandular tissue and infoldings of epithelium caused by operative procedure, or they are possibly dilated lymph-spaces. The etiology is not always determinable. The cyst varies in size from that of a small berry to that of a cherry, but may reach the size of a fetal head. It is most frequently found in the anterior vaginal wall (cyst of Gärtner's duct), sometimes in the lateral or posterior wall. A row of many cysts in the long axis of the vagina and a multiple cyst have been observed. The cyst-content is a thin mucous fluid, cloudy, yellow, or bloody, and microscopically contains mucus-cells, epithelial and blood-cells, fatty detritus, and cholesterin-crystals. The walls are composed of connective tissue, often, also, more or less unstriated muscle-tissue. The inner surface is lined with a single or more layers of cylindric, ciliated, cuboid cells, or flat epithelial cells; rarely with endothelial-like cells. Sometimes gland-acini or crypts are found in the wall; the tumor has an adenomatous character.

Echinococcus-cysts have extended from the intestinal wall into the vagina.

Myoma and fibroma develop from the fibromuscular portion of the vaginal wall. They appear as round, sometimes pedunculated, hard or, from lymphangiectatic change, soft tumors, rarely reaching the size of an apple. Their position is usually in the anterior vaginal wall.

Sarcoma.—The sarcomata found in childhood distinctly differ from those of adult life. The former always appear as polypoid, nodular, or racemose tumors, usually growing from the anterior vaginal wall (9 out of 14 cases). It is probably a congenital sarcoma, having been found at birth. It is of slow growth, or it remains as an indistinct excrescence for years, and then takes on rapid growth, extending to other deeper portions of the vaginal wall, underlying tissue, the bladder, and uterus. Histologically it is a spindle- or round-cell sarcoma. In many cases the growth is peculiar in that it contains striated muscle-cells. In the adult, between the ages of fifteen and eighty-two years, sarcoma has been found as a round, ovoid, sometimes polypoid circumscribed tumor with a smooth surface, or as a diffuse infiltration of, mostly, the lower third of the vaginal walls. The position of origin is commonly either the posterior or the anterior vaginal wall. There may be a multiple position of origin. Unlike the sarcomata of childhood, sarcoma of the adult tends to spread over the surface of the vagina, and gives metastasis to distant parts of the body. Histologically it is a spindle- or round-cell sarcoma, occasionally with myxomatous change. Also giant cells may be found. Secondary sarcoma may occur.

Carcinoma.—Primary carcinoma or epithelioma of the vaginal walls is not infrequent. It is found as a circumscribed ulcerative thickening or as a papillary excrescence, most often on the posterior wall. It is of rapid growth, quickly extending over the vaginal surface and into the deeper tissue. Secondary carcinoma, more frequent, extends from the cervix uteri or rectum by contiguity, as an auto-inoculation or contact infection, or as a metastatic growth from the uterus or ovaries. The microscopic character is that of the primary growth. We have observed a papillary adenocarcinoma as a metastatic growth from the ovary. Metastatic syneytioma malignum as a round tumor beneath the epithelium has been described. Endothelioma

arising in the endothelium of the lymph-vessels or capillary blood-vessels has been observed by Gebhard and Klein ; also a metastatic teratoma by Geyl.

Parasites which have been found in the vagina are the *Trichomonas vaginalis*, *Oxyuris vermicularis* (escaping from the rectum), *Oidium albicans*, rarely *Monila albicans*, *Monila cana*, *leptothrix*, and forms of the yeast-fungus. A long bacillus having an antagonizing power to other organisms, and forming in its growth lactic acid, is present in the normal vaginal secretion (the vaginal bacillus of Döderlein). Streptococci, the staphylococci, and various other organisms are frequently present. Pathogenic bacteria, by reason of the acid reaction of the normal vaginal secretions, here lose their virulence.

THE UTERUS.

Malformations.—The malformations of the uterus, aside from complete absence of the organ (*agenesis*), result either from faulty or incomplete fusion of, or from arrested development in, the ducts of Müller.

Malformations from Faulty Fusion.—The fusion of these ducts may completely or to a greater or less extent partially fail. The result is that either two completely or partially separated uterine halves persist, or there are two uterine cavities in one body. The division is limited to the uterine body or also extends to the cervix and vagina. The uterine cavity can in one or both halves be partially or completely obliterated.

Completely Separated Uterine Halves (Uterus Didelphys).—The uterus is composed of two completely separated uterine halves, with completely separate vaginas. Each uterine half has its tube and round ligament. There may be an atresia of the uterine lumen, and in such cases, where menstruation occurs, hematometra and eventually hematosalpinx develop. The impregnated half of such a uterus may be in the position of retroversion. The uterus didelphys has been found in the deadborn fetus and rarely in the adult (Fig. 329, a).

Partially Separated Uterine Halves (Uterus Bicornis).—The uterus is normally formed in its lower portion, and the halves separated in the upper portion. The extent of separation varies very much, from a slight depression to a deep furrow. In the slightest grade the fundus instead of being convex is concave (*uterus arcuatus*, *bifundalis*). In a more pronounced grade of separation the uterus is anvil-shaped (*uterus incundiformis*). In other instances the cervix only is normal, or a part of the cervix and the halves of the body are widely separated. Between the horns there is sometimes a distinct vesicorectal ligament. The uterine cavities are completely separated one from the other (*uterus bicornis duplex*) or unite in the cervix, there being an incomplete septum (*uterus bicornis unicollis*). In the first instance there may be a double vagina or a septum in the vagina, but commonly only one vagina is found, also only one portio vaginalis, on which two cervical canals open, one in the normal position, the other to its right or left side (*uterus biforis*).

Not rarely there is atresia of one or both uterine cavities, either of the body or cervix, perhaps with hematometra or hematosalpinx. Both horns usually functionate, menstruation taking place, and also pregnancy may occur. Pregnancy has occurred in a half with complete transverse atresia, the ovum or spermatocyst traversing the patent horn and abdominal cavities ; also tubal pregnancy.

Faulty Internal Fusion of the Uterine Halves (Uterus Duplex; Uterus Septus; Uterus Bilocularis).—When external fusion of the ducts of Müller occurs and internal fusion fails, there are present two partially or completely separated uterine cavities. The external surface of this uterus is normal, or sometimes the fundus and body are abnormally wide, and a white band may be seen extending longitudinally on the anterior or posterior surface in the median line. The wall separating the uterine halves may either be complete, extending through the body to the external os (uterus duplex septus), or be absent in the body and present in the cervix (uterus subseptus unicorporis),

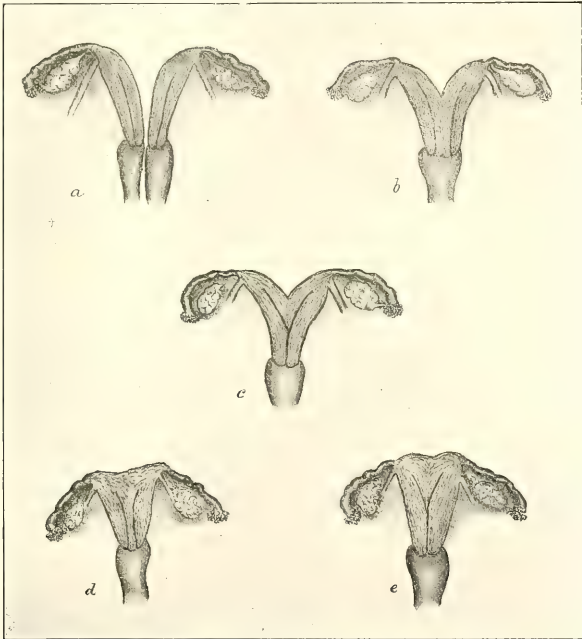


FIG. 329.—a, Uterus didelphys; b, uterus bicornis; c, uterus bicornis unicollis; d, uterus duplex septus; e, uterus subseptus unicollis.

or the opposite, absent in the cervix (uterus subseptus unicollis). In a few cases the duplication is found only at the cervical orifice. The septum which separated the uterine cavities may be incomplete, appearing as an elevation or crest-like partial septum which does not reach the opposite wall or crest. The menstrual function is present with these anomalies, except where there is an occlusion atresia.

Not rarely in double formation of the uterus both uterine halves are undeveloped, rudimentary, or through rudimentary development of one-half there is a varying degree of asymmetry of the uterus. A duct of Müller may fail to develop, or more frequently the development of one duct is

arrested in an early stage, so that it persists as a band- or cord-like rudiment, forming a uterus with one horn (uterus unicornis). The developed horn of such a uterus is somewhat shorter and thinner than the normal uterus, ends as a conical point in the tube, and is usually in the position of lateral version. The rudimentary horn, mostly the thickness of a lead-pencil, is either the same length or much shorter than the developed horn, and also ends in the tube. Complete or partial atresia of this horn may be present. The ovary of the undeveloped side is often atrophied or absent.

Agensis.—Absence of the uterus, from complete failure of development of the ducts of Müller, has been discovered only in the dead-born fetus. The vagina and greater portion of the tubes are here also absent.

After complete external and internal fusion of the ducts of Müller an arrest in the further development of the uterus (aplasia) may occur during the latter months of pregnancy (uterus *fœtalis*)-or during childhood (uterus *infantilis*), the condition persisting during adult life.

Uterus *Fœtalis*.—The uterus persists in the adult the size and form of the uterus of a newborn infant. The cervix is thicker than and twice the length of the body; the walls of the body are thin, and the corporeal endometrium is often formed into folds or plicæ. The uterus is retroposed and often sharply anteфлекed. The uterine cavity may be completely obliterated or there is more or less atresia.

Uterus *Infantilis*.—A uterus in the adult having all of the characteristics of the uterus of a newborn infant. It has the shape of the virginal uterus, but distinctly smaller; the walls are thin and soft, and the muscularis poorly developed. The tubes and ovaries in these two deformities are commonly likewise aplastic. The ovaries in the infantile uterus, however, may be normal in size and normally functionate.

A congenital bilateral split of the vaginal cervix, resembling the bilateral laceration after labor, is sometimes found in the newborn infant and in adults of undoubted virginity; also a **congenital erosion or ectropion of the vaginal cervix** in like individuals (Fischel and Penrose). The latter condition is thought to be due to imperfect development of the external os uteri, the mucous membrane of the cervical canal extending beyond the normal limits of the external os and meeting the mucous membrane of the portio vaginalis at a lower level than is normal. The cervix in these two conditions is mushroom-shaped, having a decided stalk (Fig. 330). Very rarely a congenital excessive folding of the cervical endometrium is found, resembling developing polypi. The vaginal cervix has been observed hypertrophied, the anterior of both lips, and elongated—even protruding from the vulva in newborn infants and adults, the fundus uteri remaining in its normal position. The cervical canal, particularly at the internal os, is sometimes congenitally stenosed.

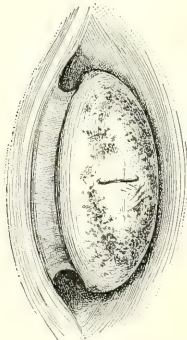


FIG. 330.—Congenital erosion of the cervix.

Congenital Malpositions of the Uterus.—The uterus may be found retroverted or retroflexed in the fetus or newborn infant, and persist in this position in the adult. Congenital retroversion or retroflexion is

thought to be due to imperfect invagination of the cervix into the vagina, a short vagina, or arrested development of the posterior wall of the uterus, the anterior wall thus outgrowing the posterior wall. From imperfect development during childhood the uterus is very frequently pathologically anteфлекed, the body, cervix, or both body and cervix, being bent forward more than the normal degree, causing constriction of the cervical canal at the internal os and obstructive dysmenorrhea at puberty. This deformity results from arrested development of the anterior wall, the posterior wall being normally developed; from atrophy; from under-development; or from imperfect invagination of the anterior lip of the cervix into the vagina. The uterus *fœtalis* is often abnormally anteфлекed. In children having lumbosacral spina bifida the uterus has been found *congenitally prolapsed*.

Hernia of the Uterus (*Hysterocele*).—The uterus in a few instances has been observed in the sac of a crural (7 cases) or inguinal (2 cases) hernia with the adnexa.

Acquired Malpositions of the Uterus.—The uterus, normally lying with its anterior surface in contact with the posterior surface of the bladder, with its long axis approximately perpendicular to the long axis of the vagina, the long axis of the uterine body inclines forward at an obtuse angle with the long axis of the cervix, may be displaced bodily forward (anteposed) or bodily backward (retroposed); bodily to the right or left (lateral position); or bodily upward (elevated) or downward (descension and prolapse). The uterine body is frequently rotated or turned backward on its transverse axis (retroverted); or it may be rotated to the right or left (lateral version); or on its long axis from right to left or left to right (torsion). The normal anterior angle of flexion may be obliterated (anteversion). The uterine body is often found inclined backward at an obtuse angle with the long axis of the cervix (retroflexion); or, rarely, flexed to the right or left (lateral flexion); or the degree of forward flexion of the body, cervix, or both cervix and body, may be increased (pathologic ante-flexion). The uterus may be turned partially or completely inside out (inversion). Two of these abnormal positions may be combined, as retroversion and retroflexion, retroversion and prolapse, etc.

Anteposition of the uterus results either from pressure exerted from below, through tumors, inflammatory or other masses in Douglas's cul-de-sac; or traction from above, through contraction of adhesions between the anterior abdominal wall and parametrium, or bladder and parametrium. *Retroposition*, through contraction of inflammatory processes behind the uterus, or, rarely, from pressure of tumors in front of the uterus. *Elevation* of the uterus is caused by the development of tumors beneath the uterus, as hematocolpos, malignant new growth, retro-uterine hematocele; or from the traction of the pedicle of an ovarian cystoma from above. *Descension* or *prolapse* of the uterus occurs in any degree from the slightest descent to its complete extrusion through the vaginal orifice. The cervix may rest on the pelvic floor (descension), protrude through the vaginal orifice (partial or incomplete prolapse); or the body and cervix be entirely extruded from the vulva (complete prolapse). Descension and prolapse of the uterus are further designated as *primary* and *secondary*. There occurs a uniform descent of the entire organ in primary prolapse; or in secondary prolapse more often the body, at least the upper portion of the body, only

partially descends, while the cervix, through stretching and elongation of the supravaginal portion, protrudes more or less from the vulvar orifice. In the first form the uterus is about normal in size, or it is uniformly enlarged; while in the latter it is much elongated, the cavity sometimes measuring 5 or 6 inches in length. Descension and prolapse result primarily from retroversion and retroflexion and their causes; injuries to the pelvic floor which destroy the normal equilibrium of the pelvic contents; relaxations of the uterine ligaments from too frequent parturition; old age and tissue-weakness; relaxation of the abdominal parietes which diminishes the retentive power of the abdomen, or any condition increasing the specific gravity of the uterus, as subinvolution after labor and congestion from inflammation. The prolapsed uterus, from disturbance of its circulation, becomes chronically congested, hypertrophied, and edematous; a hyperplasia occurs, and inflammatory changes in the myometrium and endometrium. The vaginal cervix, from long-continued edema and hyperplasia of the tissues, may be enlarged to the size of a man's fist; there is a marked ectropion of the endometrium, and often erosion or ulceration of the mucous membrane.

Retroversion and **retroflexion** often coexist, originating simultaneously, or one condition occurring primarily may induce the other. The degree of retroversion varies; the fundus uteri may be directed upward, approximately toward the promontory of the sacrum (first degree); the uterus may lie transversely across the pelvis, the cervix and fundus being at about the same level (second degree); or the fundus lies in the hollow of the sacrum and the cervix points toward the anterior vaginal vault (third degree). Retroversion and retroflexion are induced by pathologic conditions of the uterus and its supports after labor, miscarriage, or abortion—*i. e.*, any condition which increases the specific gravity of the uterus causes relaxation of the uterine ligaments and disturbs its equilibrium, as imperfect involution, lacerations of the pelvic supports and cervix, and tumors of the anterior and posterior walls of the uterus. It is often caused by the traction of inflammatory adhesions to the posterior surface of the uterus or to the adnexa. The primary cause may be a fall or other form of traumatism. From disturbance of the circulation, the tissues of the uterus thus displaced are often congested and edematous, and hyperplastic endometritis and metritis may follow.

Torsion of the uterus results from unilateral traction on the cervix, rotation of a myoma, adhesions to the fundus uteri; or it occurs with extreme torsion of the pedicle of an ovarian tumor.

Pathologic ante flexion is sometimes acquired by the traction of inflammatory adhesions from behind on the uterus at the internal os, the body and cervix thus flexing forward.

Inversion of the uterus is described as occurring in three degrees: the fundus is inverted into the uterine cavity or into the vagina; or the uterus is turned completely inside out and the fundus presents at the vulva. The vagina may also be inverted. There rarely also occurs a completely inverted uterus with complete inversion of the vagina and prolapse of the uterus. The inverted uterus may normally involute, or become congested and edematous from disturbances of the circulation, and eventually ulceration and even gangrene result. The exposed surface of the endometrium is early converted into granulation-tissue, the deeper layers of the glands showing active growth extending into the muscle-tissue. Where the uterus has been

inverted into the vagina for a great length of time, the endometrial cylindric cell covering is converted into horny squamous epithelial cells. Inversion of the uterus is caused by traction on the umbilical cord or by the practice of the Credé method of delivery of the placenta when the uterus is relaxed in the third stage of labor, or, less frequently, by traction of the pedicle of a uterine polypus attached to the fundus of the uterus.

Acquired Stenosis and Atresia of the Uterine Cavity.—The uterine cavity may be obliterated through severe puerperal endometritic processes, chemical cauterization (chlorid of zinc), and the use of the galvanocautery. Removal of the uterine mucosa with the superficial layer of the myometrium through severe curetment has been followed by atresia. Partial adhesion between opposite uterine walls not rarely occurs in old age, and where the uterine walls are brought in contact by the pressure of a uterine myoma. The cervical canal and uterine body may be obstructed by a mucous polypus or a submucous myoma. In this way a hematometra may be produced.

Hematometra.—With organic or congenital occlusion of the uterine canal in the menstruating woman the menstrual blood collects above the position of occlusion, fills and may distend the uterus to even the size of an adult head. The contents of a hematometra are a brownish-black, tar-like mass of blood containing cholesterin-crystals. The uterine mucosa from pressure is thinned, has the appearance of a serous membrane, or may be entirely destroyed. Hematometra may be combined with a hematocolpos when the atresia is in the vagina; or a hematosalpinx, the blood collection extending into the Fallopian tube. Rarely hematometra has caused rupture of the uterus.

Hydrometra.—In elderly women after the menopause, with transverse occlusion of the genital tract, a more or less serous or slightly bloody fluid may collect in the uterine cavity. There is distention of the uterus, but not to the extent above described.

Pyometra, the collection of purulent fluid in the uterine cavity, has been found caused by a suppurating tumor, mostly a malignant tumor, which obstructs the uterine canal. In the latter instance it is usually a retention of not more than a dram of purulent material.

Physometra, the distention of the uterine cavity with gas, has most often been caused by putrefaction of the fetus and its membranes during pregnancy, but may be due to the putrefaction of a malignant or other new growth.

Injuries of the Uterus.—Laceration of the vaginal cervix very frequently occurs during labor. It is said that the cervix is lacerated to some extent in every labor, but that many at once heal. They are commonly lacerations in the long axis, from the slightest division of the mucosa and fibromuscular tissue to complete splitting of the cervix to or above the internal os, and into the parametrial connective tissue or abdominal cavity. The injury is described, according to the direction and number of tears, as unilateral or bilateral laceration, laceration through the anterior or posterior lip or, many lacerations radiating from the cervical canal, as stellate laceration. Where the injury is limited to the mucosa of the cervical canal and part of the underlying fibromuscular tissue, it is designated as an incomplete laceration. In rare instances the cervix is perforated or lacerated in its transverse axis. In this way the anterior or posterior lip or the entire vaginal cervix may be torn off during labor. The vaginal cervix may be

contused, followed by necrosis, forming a deep ulcer or a communication between the cervix and bladder—vesicocervical or vesicocervicovaginal fistula. The pressure of foreign bodies, cauterization, and chemical irritants sometimes cause erosions, ulceration, and sloughing of the tissues.

Pregnancy in deformed or atrophied uteri, as the uterus arcuatus, incudiformis, unicollis, or duplex, in uteri with the scar of a previous injury, those having degenerative processes from any cause, or where the labor is obstructed, may result in incomplete or complete lacerations of the body of the uterus in any direction, forming communications between the abdominal cavity and uterus, the pelvic connective tissue and uterus, or bladder and uterus—vesico-uterine fistula.

Hypertrophy of the vaginal cervix results from disturbance of the circulation or inflammatory processes. The first acts by venous stasis and edematous swelling, as in prolapse of the uterus. The increase in size is to some extent caused by a hyperplasia of the cell-elements, but mostly an edematous swelling, a separation of the tissue-meshes by the transudate of fluid. Inflammatory hypertrophy may cause a marked increase in the size of the cervix. The vaginal and often the supravaginal cervix is thickened, hardened, the tissue rich in blood and infiltrated with small round cells. The cervical endometrium is inflamed, the glands becoming cystic, numerous Nabothian cysts being closely associated infiltrating the vaginal cervix—hyperplasia cystica portionis vaginalis.

Atrophy of the Vaginal Cervix.—The vaginal cervix atrophies, becoming smaller and shorter with the rest of the uterus and its adnexa after the natural and artificial menopause; also, it is observed in a lesser grade in the so-called lactation atrophy. Histologically the muscle-fibers have disappeared and the cervix is composed of organized connective tissue and fibrous tissue.

Ectropion with Laceration.—In deep lacerations in the long axis of the vaginal cervix, particularly the bilateral laceration, the cervix assumes the shape of a split stalk of celery, the anterior lip being drawn forward, the posterior lip backward—ectropion. The connective tissue of the cervix is hypertrophied and the mucosa of the canal swollen. Through proliferation of the mucosa the lacerated surfaces become entirely covered by cylindric epithelial cells, smaller than those lining the cervical canal. From long-continued exposure these cylindric epithelial cells are more or less, and finally completely, converted into squamous epithelial cells.

Corporeal Endometritis.—All diseases of the mucous membrane of the body of the uterus not of malignant nature, in which there are anatomic changes in the utricular glands, stroma-tissue, or both the gland and stroma-tissue, are classified as corporeal endometritis. Such diseases are truly not always of inflammatory character, being often dependent upon a simple irritation of the tissues, but the changes produced by such irritation at the present time are not definitely separable from those of an inflammation. These diseases of the corporeal endometrium are to be separated into two large groups—those which, as far as we know, are not bacterial in origin (*noninfectious endometritis*), and those which have been definitely determined to arise from bacterial infection (*infectious endometritis*).

Noninfectious Endometritis.—This form of endometritis may in a general way be said to be caused by a local disturbance of the nutrition of the uterus. It is associated with inflammation of the uterus and surrounding

structures, as the adnexa and parametrium; with new growths, as the myomata and carcinoma; it occurs with constitutional diseases, disturbances of the circulation of the uterus, chronic irritation of the genital system, and rarely it is found in young virgins where no cause is determinable. It is a disease of the sexual period of life, but is found beyond this age when there is a myoma or carcinoma of the uterus.

The mucosa is thickened, measuring not rarely a centimeter or more in diameter. It is soft in consistency. Sometimes cicatricial processes cause thinning and hardening of the mucosa. It is dark red, pale rose, or sometimes yellowish in color. The surface is smooth, diffusely nodular, or there is a circumscribed nodule with a broad base or a pedunculated polypoid outgrowth. Histologically the changes are chiefly localized either to the gland substance (glandular endometritis) or to the stroma-tissue (interstitial endometritis); or both the gland and stroma-tissue are involved (diffuse endometritis).

Glandular endometritis appears in the form of a glandular hyperplasia, the gland-tubules being actually increased in number (*glandular hyperplastic*

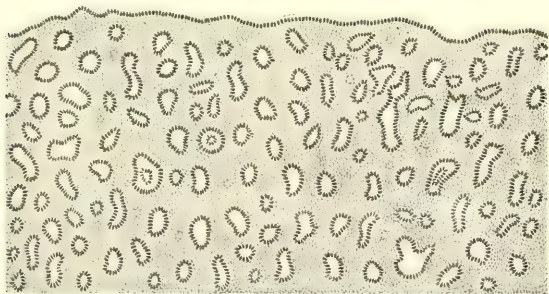


FIG. 331.—Glandular endometritis: microscopic section of endometrium removed by the curet.

endometritis), or in the form of a glandular hypertrophy, in which an increase of the epithelial gland-elements lengthens and enlarges each gland (*glandular hypertrophic endometritis*). In the hyperplastic form there occurs a glandular new growth from the endometrial surface. The mucosa is everywhere thickened, softened, and composed of glandular tissue separated by narrow areas of stroma-tissue, so that the gland-tubules are much more closely associated than in the normal endometrium. In other instances the hyperplasia is manifest as an excessive branching, division of the gland-trunks in the deeper portions of the mucosa, with the same above change in the stroma, while in the superficial portions the normal relation of the glands to stroma-tissue is usually preserved. Both forms of hyperplasia may be present in the same preparation. In the *hypertrophic* form the lengthened and enlarged glands dip more deeply into the muscularis than normal. The glands are folded upon themselves, often very tortuous—corkscrew-like—serrated, and sometimes invaginated. The endometrium is thickened, the surface smooth, and its epithelium intact. In these two diseases there is little or no hyperplasia or hypertrophy of the stroma-tissue.

Interstitial endometritis is characterized by a diffuse hyperplasia of the cell-elements of the stroma-tissue. The endometrium in the acute stage becomes swollen, soft, and spongy. The gland-tubules are widely separated, and their lumen more or less obstructed or crowded together by the hyperplasia of the stroma. A diffuse infiltration of the stroma with round cells or localized areas of round cells may sometimes be seen in the more superficial mucosa. In a later stage the round cells are converted into spindle-cell elements, and finally cicatricial contraction and atrophy of the stroma-tissue occur, with thinning and sclerosis of the endometrium, as in the atrophic changes of old age. The remaining glands are flattened, and occasionally their lumen is obstructed, forming cystic cavities. Spindle-cells in the superficial mucosa in the more acute stage may be eight or ten times the size of the normal stroma-cell, and quite identical in appearance with the decidual cell.

Exudative Endometritis.—Under this name is described a softening and edematous infiltration of the endometrium, caused by inflammatory exudate,

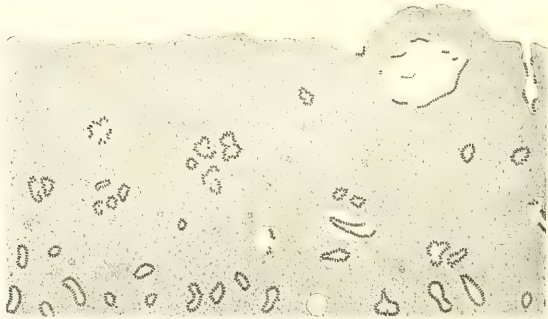


FIG. 332.—Interstitial endometritis: microscopic section of endometrium removed by the curet.

or sometimes by serous transudation into the interstices between stroma-cells. The stroma-cells are widely separated, the lymph-spaces dilated, and under high power the presence of a fine granular material resembling coagulated albumin is determinable. There is no hyperplasia of tissue. With the rupture of blood-vessels the interstices contain blood-cells—*hemorrhagic endometritis*. These exudative changes occur in the premenstrual period and cause dysmenorrhea.

Exfoliative endometritis (dysmenorrhœa membranacea) is a disease characterized clinically by the separation and discharge, piecemeal or *en masse*, at the menstrual period, of an organized membrane—the endometrium. The membrane when separated *en masse* forms a triangular sac, a cast of the walls of the uterine body, having a cervical and tubal openings. The outer surface is roughened and grayish red in color; the inner surface comparatively smooth and of a lighter color. Histologically the membrane is composed of very large stroma-cell tissue widely separating relatively few gland-tubules. The surface epithelium has almost or completely disappeared. The interstices between the stroma-cells are partially

filled with a fine granular exudate and partially with blood-elements, and here and there in the stroma are circumscribed areas of small round-cell infiltration. The stroma-cells often resemble the decidual cells, but are fewer in number and less distinctly formed, so that a differentiation is easily made. The disease is an interstitial endometritis.

Rarely during the menstrual period skin-like masses, or a sac, as in exfoliative endometritis, is discharged from the uterus, composed of coagulated fibrin (*endometritis menstrualis fibrinosa*). The coagulated fibrin is believed to be formed as an exudate at the menstrual period from an old inflammatory disease (Schönheimer).

Diffuse Endometritis.—In this disease the anatomic changes of the glandular and interstitial endometritis described are found combined in the same endometrium, either diffusely or on one area the glandular change is present and in another the interstitial. As a rule, the interstitial process predominates in the more superficial, and the glandular in the deeper, portions of the endometrium.

Fungoid endometritis is an excessive hyperplastic diffuse endometritis, the mucosa becoming many times increased in thickness, soft, spongy, with an irregular nodular or polypoid surface. There is an excessive hyperplasia of all glandular substance and stroma-tissue, the glands becoming tortuous, often ectatic or cystic.

In a diffuse or fungoid endometritis the new growth of tissue may be excessive in or limited to a small portion of endometrium. As a result



FIG. 333.—Membrane discharged in membranous dysmenorrhea.



FIG. 334.—Polypoid endometritis.

there is formed a nodular outgrowth having a broad base, or it becomes pedunculated, the pedicle sometimes being of sufficient length to allow the polypus to protrude through the cervical canal (*mucous polypus*).

Under the name *ichthyosis* or *psoriasis uteri* is described a disease characterized by a metaplasia of the cylindric surface epithelium of the endo-

metrium into a stratified squamous epithelial layer. It is thought to be caused by mechanical, chemical, or mycotic irritation. It has been found with carcinoma of the cervix, according to Wertheim and Menge, sometimes with gonorrheal endometritis.

Infectious Endometritis.—*Gonorrheal Endometritis.*—In gonorrheal infection or inflammation the endometrium is thickened (4 to 5 mm.) and the surface covered with small outgrowths, sometimes causing a warty appearance. The uterine cavity contains a thin, pure pus-secretion. Histologically there is present in the acute infection an interstitial endometritis with extensive pus and round-cell infiltration, sometimes also an inflammatory growth of gland epithelium. The pus-corpuseles are seen closely packed together in circumscribed areas, or, in less intense infection, localized to the immediate neighborhood of the glands. There is often also an exudative inflammation. The surface epithelium is absent, or, when present, the cells are separated by infiltrations of pus-cells. Wertheim has observed a proliferation of this epithelium. Gonococci are found on or in the intercellular spaces of the gland epithelium, extending from here into the subepithelial connective tissue.

The uterine cavity and endometrium may be infected with the pyogenic bacteria—staphylococci and streptococci—or with the saprophytic micro-organisms, causing an extensive suppurative destruction of the endometrium, the uterine walls being covered with an abscess membrane and the uterine cavity more or less filled with pus (*endometritis putrida* or *pyometra*). Such infections occur with putrefying fibromyomata and carcinoma, or the infecting organisms are carried into the uterus by means of instruments.

Pseudomembrane formation, a croupous or diphtheritic inflammation of the uterine mucosa, aside from the puerperal form, is very rare. It has been observed during the course of typhoid fever, cholera, small-pox; also with putrefaction of uterine carcinoma. A true diphtheritic inflammation, infection by the Löffler bacillus, has not been determined in the non-puerperal uterus.

Erosion of the vaginal cervix, a metamorphosis of the mucosa of the portio vaginalis into tissue more or less resembling the inflamed cervical endometrium, is found with and evidently arises from cervical catarrh. A sharply defined, intensely red membrane-like covering is seen extending from the external os, and to a varying extent covering the vaginal cervix, rarely even to the vaginal vault. The surface of the erosion is smooth (*simple erosion*), finely papillary (*papillary erosion*), or nodular from the presence of gland-cysts (ovula Nabothi) (*follicular erosion*). In the *simple erosion* there is a metamorphosis of the squamous surface epithelium into cylindric epithelium without an increase in the glandular substance. In the *papillary erosion* the same change occurs, with also the formation of glands of the cervical type in the immediately underlying tissue, which, through close association and ingrowth or outgrowth of the interglandular stroma-tissue, forms papillary excrescences. The *follicular erosion* is characterized by the presence of numerous Nabothian cysts, forming nodules on the surface, the cystic formation being induced by bending, constriction, or occlusion of the gland in the healing of the erosion. Such cysts may be so closely associated and numerous that little interglandular tissue remains, causing hypertrophy of the cervix (cystic cervical hypertrophy). The epithelial cells lining the cyst

becomes cuboidal, flattened, or separated. Occasionally a hyperplasia of the cells occurs, forming a small epithelial outgrowth in the cyst. The inflammatory changes are identical with those of cervical endometritis. Erosion of the cervix is in no sense a destructive process.

Cervical endometritis, a catarrhal inflammation of the cervical mucosa with profuse secretion, results from poor nutrition and constitutional disease, laceration of the cervix, or gonorrheal infection. The mucosa is reddened, swollen, its folds thickened and rounded and covered with a tenacious mucus. There is present a small amount of glandular hyperplasia. The gland-acini are dilated and filled with mucus and desquamated epithelium. The stroma-tissue in the acute stage is diffusely infiltrated with small round cells, and sometimes many mast-cells are seen in the fibromuscular wall. The discharge is a tenacious mucus from the Nabothian

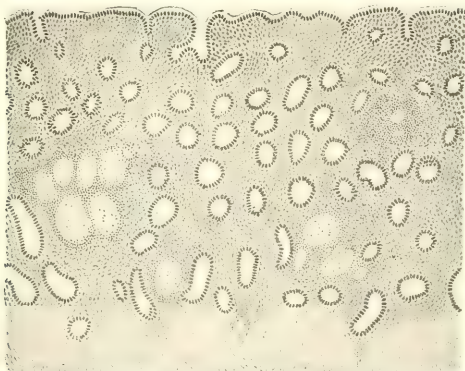


FIG. 335.—Miliary tuberculosis of the endometrium and glandular endometritis.

glands, or in the more acute and intense inflammations, combined with serous transudate from the vessels, it is mucoseropurulent.

Mucous Polypus.—Frequently in cervical endometritis there is a circumscribed hyperplasia of the mucosa-elements, forming nodular outgrowths or pedunculated polypi. Such a polypus is composed of stroma-tissue containing tortuous, often cystic, glands, having highly cylindric epithelium, with basal nuclei. The cylindric surface epithelium through insult becomes squamous and stratified, or it is destroyed by ulcerative processes.

Tuberculosis of the endometrium occurs as a secondary descending infection from a tubercular peritonitis or tuberculosis of the tubes, and, possibly, very rarely as a primary infection, the infection taking place through the cervical canal or lymphatic system. The disease, as a rule, is limited to the corporeal endometrium, but may, in a late stage, extend secondarily to the cervical endometrium. It appears as a chronic diffuse miliary tuberculosis in the more superficial mucosa or diffusely infiltrating every portion of the mucosa, or it has been found as a diffuse fibroid tuberculosis. In the first form, with caseation and confluence of the tubercles, the

mucosa is to a greater or less extent destroyed and the surface of the underlying myometrium covered with tubercular granulation-tissue. In the second form the superficial epithelium and glandular tissue are destroyed, the stroma is converted into fibrous tissue containing areas of calcification and miliary tubercles having occasionally a giant cell. A tubercular infec-

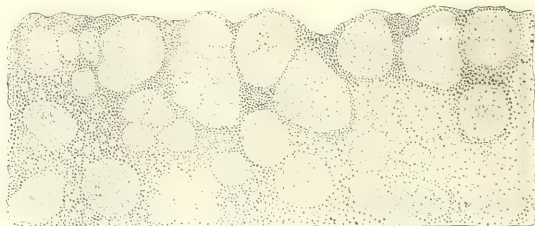


FIG. 336.—Advanced fibroid tuberculosis of the endometrium.

tion of a mucous polypus is described. Bacilli are found in the tubercles and discharge.

Ulceration or **ulcers** of the portio vaginalis not of specific nature are mostly caused by the application of chemical irritants, pressure necrosis of foreign bodies (pessary), or injury to the exposed cervix in prolapse of the uterus. It is occasionally found with erosion of the cervix. The changes here are identical with ulcerations of other mucous membranes.

Syphilitic infiltrations and chancre of the vaginal cervix are rare.

They have the same character as those of the skin and mucous membrane of the mouth.

Tuberculosis of the cervix is extremely rare, appearing either as an ulceration or ulcers of the portio vaginalis or cervical endometrium, as a tubercular papillary endocervicitis and papillary erosion, or as a miliary tuberculosis of the portio vaginalis. In the first form, a single large ulcer or multiple minute ulcers are found on the portio vaginalis, mostly surrounding the external os uteri, or, when far advanced, there is more or less extensive ulcerative destruction, through caseation necrosis, of the cervix.

The tubercular endocervicitis involves mostly the lower half of the cervical endometrium, and extends into the portio vaginalis as an erosion, sometimes as a papillary outgrowth, which in one instance reached the size of an apple. The cervix is hypertrophied. It is a chronic diffuse tuberculosis, and in the late stage may become, through caseation necrosis, the ulcerative form. Miliary tuberculosis, as minute

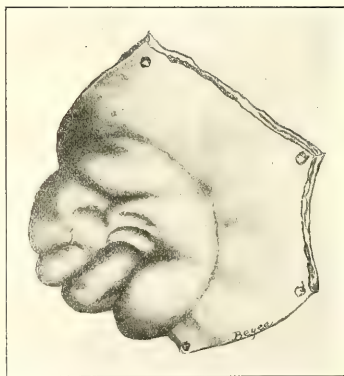


FIG. 337.—Tubercular papillary erosion.

tubercles scattered diffusely over the portio vaginalis, has been described as being present with far-advanced tuberculosis in other parts of the body. Bacilli are usually to be discovered in the tissue. Tuberculosis here, except in 3 cases (Friedländer, Kauffmann, and Michelas), has been a secondary infection.

Metritis.—**Acute metritis**, acute inflammation of the myometrium, may sometimes take place in the nonpuerperal uterus from the infection of pyogenic organisms, mostly as an acute gonorrheal infection. The uterus in enlarged, the peritoneal covering mottled-like or diffusely reddened, and the muscle-wall much softened. On section the muscle is more rose colored than normal, and edematous. There is a hyperplasia of the perivascular connective tissue, with a profuse leukocytic infiltration and striated-like small round-cell infiltration extending through the wall to the peritoneum, or in less severe inflammation the small round-cell infiltration is localized to the central portion of the wall. Rarely a gonorrheal metritis ends in the formation of multiple intramural small abscesses containing gonococci. Gonococci in acute infection may be found intracellular and extracellular throughout the muscular wall.

Chronic metritis follows acute inflammation, or an inflammatory change occurs in a uterine hyperplasia due to persistent passive hyperemia, as in malposition, subinvolution of the uterus, chronic endometritis, and with uterine or adnexa new growths. The body-cervix, usually both body and cervix, are enlarged; the consistency of the muscle-wall increased; the cut surfaces show undulations and are pale gray in color. Histologically there is a chronic inflammatory perivascular connective-tissue hyperplasia, with myohypertrophy. The connective-tissue hyperplasia increases with the duration of the disease and age of the woman.

Atrophy of the uterus occurs with the natural and artificial menopause, from prolonged lactation (lactation atrophy), and in chronic diseases, as chlorosis, phthisis, diabetes, myxedema, Addison's and Basedow's disease, nephritis, and leukemia, and, according to Döderlein, rarely with chronic gonorrhea. It is either a concentric or excentric atrophy; in the latter the uterus remaining normal in length and the walls becoming thinned. The atrophy begins in the body and extends to the cervix. The uterus is small, hard, and dense; in the excentric form sclerotic and tough. A compression atrophy of the walls occurs with hematometra. Histologically there is a numerical myocellular atrophy; the muscle-cells are also smaller than normal and there is a predominance of fibrous connective tissue.

Fatty degeneration of the subserous muscle-wall may occur with purulent perimetritis and in gonorrheal or tubercular abscess formation. Amyloid degeneration is described by Virchow.

Vascular changes in the myometrium are rare. In the atrophied uterus the arterial walls frequently show hyaline degeneration; also sometimes calcification is present. Arteriosclerosis, atheromatous uteroplacental vessels, aneurysm of the vessels of the placental site, and hyaline degeneration with osteomalacia are described.

New growths of the Uterus.—*Fibromyoma*, *fibroma*, and *myoma*, described as myoma, tumors composed of connective and muscle-tissue, the one or the other predominating, are frequent new growths of the uterus, growing mostly from the myometrium of the body, and occasionally from the fibromuscular wall of the cervix uteri. They are multiple or often

single spheric or ovoid nodules, varying in size from a pinhead to an adult's head, but may reach enormous dimensions. Arising in the myometrium, they develop in the direction of least resistance, and are designated from their position and relations as subserous, interstitial, and submucous myoma. Myomata are of slow growth, the fibroma being slower than the myoma. They may be said to be tumors of the menstruating uterus, the growth ceasing or the tumor atrophying at the menopause. Occasionally the growth continues after the menopause.

Subserous myomata are multiple or single nodules or pedunculated tumors covered with peritoneum, attached to the external surface of the uterus by a broad base or pedicle. They are also immediately surrounded by loose connective tissue. The peritoneal covering is firmly attached. Torsion or rotation of the pedicle, and through torsion separation of the tumor from the uterus, may occur. Through pressure necrosis or inflammatory adhesion the tumor may become attached to surrounding structures. A subserous myoma may arise from the lateral wall of the uterus and develop between the layers of the broad ligament (intraligamentous myoma).

Interstitial myomata occur as circumscribed tumors, surrounded by and attached to the myometrium by a loose connective-tissue capsule. Rarely the tumor is closely attached to the muscle-tissue, so that no connective-tissue capsule is discernible; also, more rarely, there is a diffuse muscular tumor of the uterus.

Submucous myoma is a myoma in which the greater surface of the nodule protrudes into the uterine cavity as a pedunculated interuterine polypus, having a pedicle of varying length. The tumor is soft in consistency, has a rich blood-supply, and is covered with loose connective tissue, and to a greater or less extent with the endometrium. The pedicle is formed of connective tissue with a few muscular fibers, and contains a few blood-vessels. Through inflammation the tumor may become adherent to the surrounding uterine wall.

Cervical myoma, forming 5 to 6 per cent. of the uterine myomata, arises in the infravaginal or supravaginal cervix, the former developing in the vagina, the latter usually into the retrocervical connective tissue.

In interstitial and submucous, often in the subserous, myomata there is an associated muscular hypertrophy of the myometrium, quite similar to the physiologic hypertrophy, the uterine walls being thickened and the uterine cavity to a greater or less extent enlarged and distorted. On section the tissue is white (fibrous tissue) or rosy (muscle-tissue) in appearance, composed of bundles of fibromuscular tissue arranged more or less concentrically about small areas. Large arteries and venous sinuses are found in the connective-tissue capsule, and a few small blood-vessels in the tumor substance. The consistency of the tumor varies from soft, in young pure myoma, to hard fibromyoma, and stony-hard fibroma. Histologically they are formed of muscle-cells having spindle-nuclei and homogeneous protoplasm, of muscle-tissue bundles separated by loose connective tissue poor in cells, or in other cases dense connective tissue. Mast-cells, long, spindle, ovoid, or round, are present in varying numbers, mostly in the neighborhood of blood-vessels.

The *endometrium* in interstitial and submucous and sometimes in subserous myoma shows hyperplastic change, a hyperplasia of the gland substance, of the stroma-tissue, or of both. In those having a large surface protruding

into the uterine cavity the endometrium is stretched over this surface, and is thinned and atrophied. The endometrium may undergo malignant adenomatous change.

The *Fallopian tubes* with large myomata are often the seat of an endosalpingitis which is characterized by the presence of mucus, separated epithelium, swelling of the mucosa rugæ, hemorrhage into the mucosa, and edematous and exudative infiltration into the mucosa. Also an interstitial salpingitis occurs, the muscular wall being thickened (Fabricius).

The *ovaries*, according to Bulius, always show more or less distinct change. They are enlarged through increase in size and number of the follicles, and partially through hyperplasia of the interstitial tissue; the stroma is more or less infiltrated with small round cells; the vessels show hyaline degeneration, with stenosis or obliteration of their lumen; there is a premature disappearance of the primordial follicles; the corpora fibrosa are increased in number.

The myoma itself very often undergoes pathologic changes, most of which are due to disturbance of the nutrition. *Atrophy* results from the physiologic involution of the genital system during the puerperum, climacterium, or after bilateral oöphorectomy. The muscle-cells become smaller and fewer in number, and the proportion of connective tissue is greatly increased and converted into a solid, hard, callous mass, having the character of cicatricial tissue. In this way a myoma may completely disappear.

Calcareous infiltration occurs with advanced atrophy, sometimes to the extent of forming a calcareous mass (uterine or womb-stones). A conversion of the myoma into bony structure (osteomyoma) is described.

Fatty degeneration is frequently found in the interstitial and submucous, rarely in the subserous, tumors after pregnancy, or in those of dense consistency.

Anyloid degeneration of the tumor and myometrium, or tumor alone, may occur.

Maceration of the tumor may be present with acute disturbance of the circulation, the tissue becoming soft, turgid, infiltrated with blood, and finally brownish green in color.

Myxomatous degeneration is very frequent in the interstitial, submucous, and particularly in the intraligamentous, tumors. It begins as a softening of the tissue, the intercellular substance undergoing mucoid change, or, further advanced, the consistency of the tumor is cystic, and finally cavities are formed in the center of the nodule, filled with mucoid substance. Myxomatous degeneration causes the tumor to increase rapidly in size.

Inflammation, necrosis, and gangrene of submucous myoma and polypi, often of interstitial and subserous myoma, are frequent, the infecting organism entering through the vagina, or, in case of the subserous myoma, from the intestine. Coagulation necrosis in the center of a nodule, forming a cavity, may take place.

Thrombi are found in the blood-vessels, particularly with torsion of the pedicle and incarceration. Extensive thrombosis causes edematous infiltration; also edema occurs in any case in which the circulation is obstructed. The vessels are also obliterated with the pathologic changes described.

Telangiectatic change, the tissue being infiltrated with numerous dilated large blood-canals, is now and then found (*telangiectatic myoma*). Also the lymphatic vessels may be dilated, the tumor containing numerous cystic

cavities lined with endothelial cells (*cystic myoma*). The fluid contents of such cysts coagulate on exposure.

The *etiology* of the myoma of the uterus is unknown. According to Virchow, and this is the theory generally accepted, they are growths derived from the unstriated muscle-fibers of the myometrium; therefore a hyperplasia of the uterine parenchyma. Other theories are, that they arise from round cells found surrounding capillaries undergoing obliteration, from the muscle-wall of the blood-vessels, or that they have a parasitic origin.

Adenomyomata are a rare form of myomata of the uterus, containing gland-elements. The epithelial canals in these tumors are either derived from the uterine mucosa or the remains of the Wolffian body (Recklinghausen). In the first instance the tumor is centrally located, either in the anterior or posterior or lateral uterine wall, and has, except for the presence of glandular structure, the usual characteristics of a myoma. Those derived from the remains of the Wolffian body are found developing on the posterior surface of a uterine cornu, or less often in the tube, and when small also in the peripheral layers of the myometrium. The chief mass later is interstitial and partially submucous in position. It is strongly adherent to the surrounding tissue, no capsule being determinable. It occurs in the following forms: A tumor dense in consistency, in which the muscle-tissue is in excess of the adenomatous tissue; a cystic tumor with distinct numerous macroscopic cavities; a softer adenomyoma, in which the adenomatous tissue is in excess, with rich germinal connective tissue; and a very soft tumor with dilated blood-vessels—telangiectatic or angiomatous adenomyoma. The tumor arises from single or numerous diffuse centers. They are often kidney- or roset-shaped, and have a cortical and medullary zone. Histologically the tumor is composed of muscle-tissue containing epithelial canals, among which a chief canal is to be differentiated, the others extending from this and ending in an ampulla, one before another in a pectinate form. One such system is seen under another. The gland-canals are embedded in germinal connective tissue like that forming the ground substance of the uterine mucosa; but where the canals are dilated into cysts this connective tissue is absent and the cyst-wall is immediately surrounded by muscle-tissue. The cystic cavities may contain pigment or bloody fluid. The muscle-tissue, it is believed, is derived from the muscle-wall of the gland-canals.

Rhabdomyomata have been described as pedunculated polypi of the cervical canal, which always contain sarcoma-elements, and through metastasis cause death.

Through metaplasia of myoma or extension of proliferating growths from the neighboring tissue into a myoma, mixed tumors are formed—myo-chondroma, myo-osteoma, very rarely myosarcoma, not infrequently, also in the latter manner, myocarcinoma.

Myosarcoma, the metaplasia of myoma into sarcoma, forms tumors rapidly increasing in size, which on section have a more homogeneous appearance, the fasciculi of the myoma having disappeared. The sarcoma-tissue quickly undergoes necrotic change, sometimes to the extent that only a shell of softened tissue remains. It often contains blood extravasations and apoplexies. The sarcomatous disease extends to and infiltrates neighboring healthy tissue. The sarcoma-cells are large, irregular in form, and the nuclei rich in chromatin. Often many nuclei are seen in one cell. The

spindle-cells retain their form for a long time, indicating their origin in the myoma-cell. Sanger believes that all myomata containing giant cells and myoclasts have sarcomatous degeneration.

Myocarcinoma are thought to be formed either through inversion of the mucous-membrane polypus-like growth into the myoma-tissue, or it is a carcinoma developing from the glandular structure of an adenomyoma, or possibly there is a metaplasia of myoma-elements into carcinoma-elements, as in a case reported by Rolly.

Carcinoma.—*Carcinoma of the portio vaginalis*, or that portion of the vaginal cervix covered with squamous epithelium, appears as a squamous or cylindric-cell carcinoma.

Squamous-cell carcinoma originates either in the squamous epithelium covering the normal portio or in new-formed squamous epithelium of an erosion. It consists in an ingrowth and branching of this epithelium, forming large, sometimes small, squamous-cell alveoli in a stroma usually infiltrated with small round cells. Coincident with the ingrowth there is a general branching outgrowth of the stroma and epithelium, forming papillæ, nodules, or cauliflower outgrowths. Early the portio surface is covered with granulation-tissue, fibrin-masses infiltrated with round cells, or the squamous stratified surface epithelium remains intact. The horny layer of epithelium is often poorly developed, and therefore epithelial pearls are not frequent. The outgrowth of stroma and epithelium may be absent and the carcinoma has an infiltrative character. Rarely the squamous epithelial change remains for a long time superficial, through necrosis an ulcer is formed, and the carcinoma is found separated from the underlying tissue by a thick wall of small round-cell infiltration—rodent ulcer.

Cylindric-cell carcinoma originates in the new-formed surface cylindric cells or glands of an erosion of the cervix. In the former the cylindric surface epithelium undergoes metaplasia into many layers, and ingrowths and alveoli are formed in the stroma-tissue entirely independent of the glandular structure, or rarely the glands are to a small extent also involved. In the latter form the glandular elements undergo metaplasia, mostly combined with a metaplasia of the superficial cylindric epithelium, forming an adenocarcinoma of the portio vaginalis.

The macroscopic character of carcinomata of the portio vaginalis cannot be differentiated. They appear as infiltration enlargements, with papillary, nodular, or cauliflower-like outgrowths, perhaps the size of a double fist. In other instances the growth extends only into the deeper structures, infiltrating the stroma and thickening the vaginal cervix, the stratified squamous epithelium remaining intact and the surface smooth and unchanged. Or rarely the *ulcus-rodens* form is observed in squamous-cell carcinoma.

The consistency of the growth varies, depending upon the proportion of fibrous stroma-tissue, being sometimes hard, at other times soft. The surface epithelium sooner or later undergoes fatty degeneration, and through putrefaction a more or less extensive carcinomatous ulceration occurs. A carcinomatous infiltration of a myoma of the cervix—myocarcinoma—has rarely been observed, and more rarely chondrocarcinoma arising from the tissue of the portio vaginalis or a fibroma of the cervix.

Carcinoma of the portio vaginalis extends to the vagina, thence into the vesicovaginal or rectovaginal connective tissue; from the cervical stroma-

tissue into the supravaginal cervix, and thence into the loose pericervical connective tissue and to the iliac lymph-glands. Contact-metastasis to the vaginal walls may occur.

Carcinoma of the cervix, originating in the endometrium, occurs most frequently in the form of a cylindric-cell, rarely as a squamous-cell, carcinoma. The cylindric-cell form arises either in the cylindric surface epithelium or in the glands of the endometrium. It has the macroscopic and microscopic character of that described of the portio vaginalis. The squamous-cell carcinoma arises in the squamous epithelium which is not infrequently found abnormally extending over the endometrium, beyond the limits of the external os. Also a circumscribed carcinomatous infiltration may be found developing in the deeper portion of the cervical fibromuscular wall, beyond the normal limits of the endometrium and squamous epithelium of the portio vaginalis. It is an adenocarcinoma, or sometimes the alveoli are formed in lymph-channels—a lymphatic carcinoma. Carcinoma in this

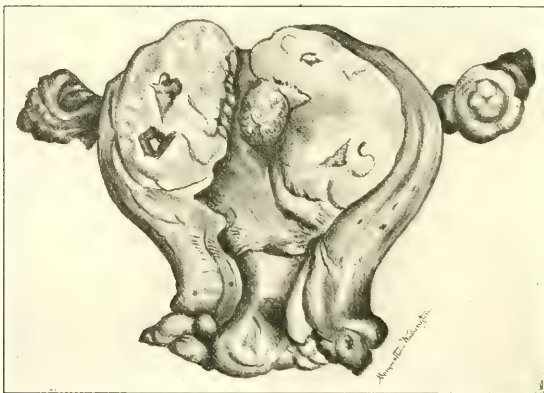


FIG. 338.—Cancer of the body of the uterus: a large single cancerous nodule (c) in the anterior wall has been divided.

position is believed to develop from an abnormally deep ingrown gland. Veit and Amann have considered it an endothelioma.

Cervical carcinoma, both that of the surface epithelium and of the gland substance, infiltrates the stroma and fibromuscular tissue of the cervix in every direction, extending more or less into the myometrium of the lower uterine segment, into the pericervical connective tissue, and to the iliac lymph-glands. The cervix, both in diameter and length, is enlarged, often to three times its normal size. Retrograde changes occur, destroying the portio and excavating the cervix surrounding the canal, or the carcinoma-growth may fill the cervical canal and form an outgrowth on the portio vaginalis. The cervical canal may be obstructed by the growth and a pyometra be formed. An associated adenocarcinoma of the cervix and body of the uterus has been observed (Cullen). Metastasis to distant organs in carcinoma of the cervix or portio vaginalis is extremely rare.

Malignant adenoma is a rare new growth of the cervix. The cervical

tissues are extensively infiltrated with numerous branching, often communicating, sometimes cystic, dilated atypical glandular structure. The acini are lined with a single layer of fine cylindric epithelium. The cervix is hypertrophied, and in 2 instances there was a polypoid outgrowth. The malignant adenomatous structure persists for a long time, but finally, through proliferation of the epithelium, becomes an adenocarcinoma.

Carcinoma of the body of the uterus develops either from the utricular glands or cylindric surface epithelium of the corporeal endometrium. It is a cylindric-cell, or very rarely a squamous-cell carcinoma.

The cylindric-cell carcinoma commonly begins as an excessive atypical new growth of the glandular structure, as a malignant adenoma, which, in some instances early, in others only late, through proliferation of the gland-cells into many layers, becomes an adenocarcinoma. Rarely there occurs a rapid epithelial-cell proliferation of the gland-elements into a medullary form without the malignant adenomatous or adenocarcinomatous character—carcinoma glandulare simplex (Gebhard).

The surface of the corporeal endometrium is seen covered with a diffuse or circumscribed outgrowth, which to a greater or less extent fills and distorts the uterine cavity. These growths are soft, pale-rose nodules with smooth surface (nodular carcinoma); they are warty-like papillary outgrowths (papillary carcinoma), or the surface of the growth is covered with closely-packed-together soft, floating, fine thread-like villous growths (villous carcinoma). A polypoid character is also described.

Carcinoma here tends generally to spread diffusely over the surface, involving the entire corporeal endometrium, rather than to extend into the underlying tissue, or it forms circumscribed outgrowths. The carcinomatous disease is limited to the body of the uterus, being sharply defined at the internal os. The cervix and vagina may be very rarely involved late in the disease. The myometrium is much thickened and the uterus enlarged; except in the senile uterus, the size of the organ may remain unchanged and the walls become thinned. As the disease advances the myometrium is slowly infiltrated to the peritoneal covering, which tissue forms a strong barrier to further advancement. Retrograde changes sometimes occur, with the formation of deep crater-like ulcerations, the edges of which have a papillary or villous appearance. Lymphatic metastasis to distant parts, the vagina or ovaries, is very rare.

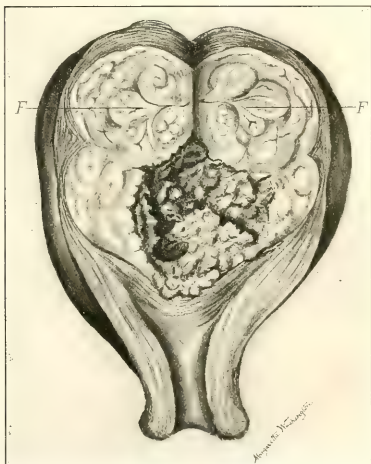


FIG. 339.—Advanced malignant adenoma of the body of the uterus. A fibroid tumor (F) is in the fundus.

Malignant Adenoma.—In malignant adenoma of the body of the uterus the tissue is composed of closely-packed-together gland-canals, running in a parallel direction from the surface of the endometrium inward and com-

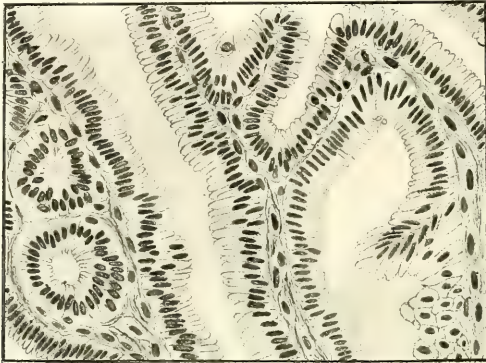


FIG. 340.—Malignant adenoma of the body of the uterus.

municating one with the other; or of numerous branching, divided and subdivided, gland-trunks; or, further, there are an extraglandular evert ing and intraglandular inverting of the epithelial cells. This malignant adenomatous character may persist occasionally until the myometrium is exten-

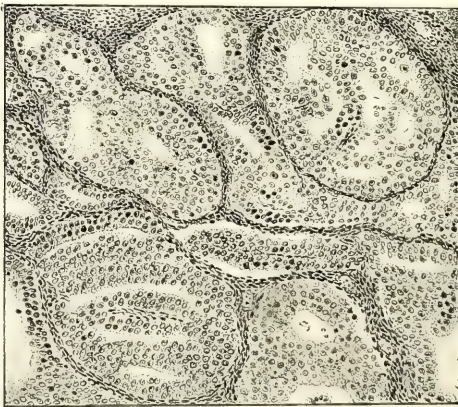


FIG. 341.—Adenocarcinoma of the body of the uterus.

sively destroyed, as in Fig. 340. There is little interglandular or stroma-tissue, it being in some places only a cell in thickness. The gland-canals are lined with a single layer of highly cylindric epithelium, closely packed together, so that the shape of the cells is often distorted. The position of

the nuclei differs, being sometimes seen toward the base, at other times toward the ciliated extremity of the cell. Nuclear figures are usually present to a considerable extent. The cilia have mostly disappeared.

Adenocarcinoma.—The conversion of malignant adenoma into adenocarcinoma may be localized or diffuse. The adenocarcinoma becomes an alveolar carcinoma, and finally the stroma disappears and the tissue of the growth is entirely composed of carcinoma-cells. The stroma-tissue in the malignant adenoma and adenocarcinoma is composed of connective tissue having a fibrillary character. Small round-cell infiltration is present, mostly with destructive secondary change.

Squamous-cell Carcinoma.—Rarely (3 positive cases) in the disease described as ichthyosis of the uterus (page 1033) there has occurred an ingrowth and branching of the metaplastic stratified squamous epithelium

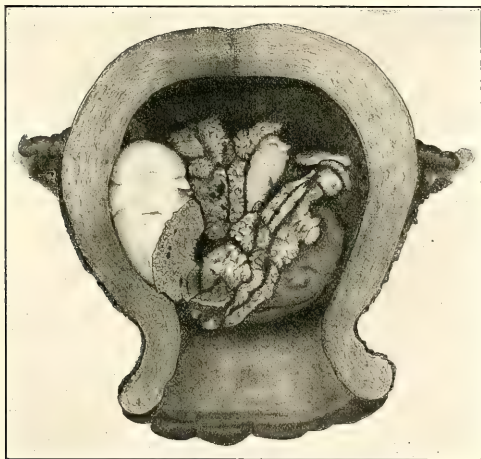


FIG. 342.—Diffuse sarcoma of the corporeal endometrium.

into the deeper tissues, with the formation of a squamous-cell carcinoma, which is quite identical with that of the portio vaginalis.

Sarcoma of the uterus develops in the body, rarely in the cervix, of the uterus, and from the connective tissue of the endometrium—sarcoma of the endometrium; or from the fibromuscular elements of the myometrium—sarcoma of the myometrium.

Sarcoma of the endometrium appears either as a cock's-comb-like ragged or smooth-surface nodular outgrowth protruding into the uterine cavity (Fig. 342), or as a diffuse infiltration and thickening of the endometrium. Also sometimes developing from a circumscribed area, it has a polypoid character. The tissue is white, brain-like, very soft, crumbling, and often containing, particularly toward the center, recent or old apoplexies. The disease soon extends into the uterine wall, the peritoneum is perforated, and the growth protrudes into the peritoneal cavity, usually as a polypoid tumor.

Sarcoma of the myometrium is found as a large or a small, single or multiple, circumscribed area of pale softened tissue. The large nodules extend toward the endometrium or peritoneum and protrude on the surface. In many instances such nodules are intra-uterine polypi, fibromyomata degenerated into sarcoma—myosarcoma—and are early surrounded by a connective-tissue capsule.

The myometrium in both forms is thickened, and the uterus often enlarged to the size of a five-month pregnancy, or there is a sarcomatous thinning of the walls. With obstruction of the cervical canal secretions and blood may be retained in the uterine cavity, also pus.

Sarcoma of the cervix occurs either as a diffuse growth thickening the cervical walls or as a soft nodule with ragged surface protruding into the cervical canal or from the external os. The former arises in the fibromuscular elements of the cervical wall, the latter in the connective tissue of the cervical endometrium.

Sarcoma of the portio vaginalis, which is very rare, develops as a nodular thickening of the cervical lips, the mucosa remaining intact, or as a papillary outgrowth similar to the cauliflower carcinoma. It has been observed as a multiple polypoid growth attached to the mucosa just within the external os, and resembling a hydatidiform mole. Histologically sarcomata of the uterus are large or small round-cell sarcoma of the endometrium or connective tissue of the myometrium; spindle-cell sarcoma of the muscle-cells or intermuscular connective tissue, giant-cell sarcoma, the round- or spindle-cell form having many giant cells, or the tissue is composed of giant cells. The cells may also be ovoid in shape. The round-cell form may have a lymphoid character. In rare cases the matrix of the tumor is the blood-vessel walls, which with proliferation of the blood-vessels forms an angiosarcoma. Myosarcoma occurs as described; adenosarcoma, melanosarcoma, and carcinosarcoma have been described developing from the uterus. In the sarcoma of the portio vaginalis having a multiple polypoid formation, the intercellular substance shows an abundant mucoid change, due to venous stasis or metaplasia of mucoid tissue—myxosarcoma. Also in this last growth cartilaginous tissue has been found—chondrosarcoma. Sarcoma of the body of the uterus may be associated with carcinoma of the cervix.

Hemorrhagic destruction, as large or small apoplexies, is frequent; fatty and hyaline degeneration may occur.

The disease extends through the uterine wall by continuity, or more often the myometrium is converted into sarcoma-tissue, the peritoneum is perforated, and secondary sarcoma develops on the peritoneum, in the connective tissue of the broad ligament, and sometimes the tube-wall and ovaries are affected. Metastasis to distant organs is very rare. Metastasis has most often taken place to the lungs. Implantation metastasis is less frequent than in carcinoma. The malignant character in many cases of sarcoma is clinically for a long time latent, and then with rapid increase in the size of the growth the malignancy becomes active. Sarcoma of the uterus occurs at any age—as early as two years, more frequently after puberty, and particularly at the climacteric period.

Endothelioma of the uterus has been described as developing from the mucosa of the portio vaginalis (twice), in the corporeal endometrium (once), and in the mucosa covering a submucous sarcoma (once).

Foreign Bodies and Parasites.—Hairpins, knitting-needles, and

various sharp instruments have been found in the uterine cavity, introduced in the practice of criminal abortion. Also, in the practice of masturbation, various other instruments.

Secretions have escaped into the uterus in perforation or rupture of the uterine walls. In labor or abortion the fetus, its head, pelvis, or an extremity, has been retained in the uterine cavity.

Echinococci in the cavity or echinococcus-cysts in the wall of the uterus have been observed. Single instances of tapeworm and *Ascaris lumbricoides* are described.

Pathology of the Uterus in Pregnancy, Labor, and the Puerperium.—Injuries.—The pregnant uterus has quite frequently been more or less injured or perforated by instruments in criminal abortion, the perforation being in the portio vaginalis, the posterior wall of the uterus just above the internal os, and rarely at the fundus. Gunshot wounds, perforation and laceration by the horns of an enraged bull, and similar traumatism, are reported. Reference has previously been made to lacerations and contusions of the uterus during labor.

Decidual endometritis (inflammation of the decidua during pregnancy) follows a pre-existing endometritis, results from local infection of the decidua, or is part of a general dystrophy following an infectious disease. The decidua vera and serotina, sometimes also the reflexa, are either diffusely and evenly thickened, measuring perhaps 1 cm. in diameter, or there is an irregular tubercular thickening or polypoid swelling of the decidua. The tissue is dense in consistency, the yellowish opaque color has disappeared, and it has a cicatricial appearance. The surface may rarely be covered with pus, and the underlying tissue intensely reddened. In some cases the decidua is converted into a soft, spongy mass of tissue, edematous and containing numerous cavities. Transudate and secretion from the glands, as a mucoserous fluid, can collect between the vera and reflexa and be discharged periodically—*hydrops hæmorrhæa gravidarum*.

Histologically the process is chiefly an interstitial inflammation. The decidual cells are quantitatively increased, sometimes enlarged, and then show fatty change; often they are infiltrated with round and spindle-cells, finally with bundles of fascicular connective tissue, even to scirrhous change. The glands may be slightly increased in number and dilated. In the acute form, particularly the acute infectious inflammation, there is a diffuse and often extensive small round-cell infiltration. The round-cell infiltration is commonly localized to the superficial layers of the decidua, and the deeper layers contain numerous collections or strata of leukocytes. In other instances the disease is an exudative inflammation, the decidual cells being widely separated.

Puerperal endometritis occurs as a saprophytic infection of the mucosa surface, characterized by putrid processes (putrid endometritis), and as a septic infection, with purulent or diphtheritic change in the mucosa (septic endometritis). Both forms may be combined in the same uterus.

Putrid endometritis (*endometritis putrida*) is caused by the infection of anaërobic bacteria, the biology of which is not as yet determined. The *Proteus vulgaris* or *Bacteria coli commune* may be the cause. The uterine cavity is found more or less filled with a pulpy, discolored, sometimes brown or greenish, bad-smelling mass. After this is removed the uterine surface is covered with similarly discolored flakes and shreds of necrotic tissue,

which layer of tissue on section is sharply defined from the healthy myometrium. At the placental site unorganized thrombi, through the putrefaction, are converted into coffee-like masses of degenerated blood. Physometra may be produced by the action of the bacteria on the albuminous substances. Histologically the surface or putrefying layer of tissue is composed of a cloudy transparent mass of tissue, the nuclei of which fail to take the stain. In this zone and slightly beyond it are found the various micro-organisms. Then follows a layer, a reaction zone, separating the healthy myometrium from the diseased tissue, which is composed of necrosing decidual tissue profusely infiltrated with small round cells and leukocytes. A few round cells are seen in the myometrium.

Septic endometritis (*endometritis septica*) is caused by streptococcus, very rarely by Staphylococcus albus or aureus infection of the endometrium. Often there is a mixed streptococcic and staphylococcic infection. The presence of these bacteria and their toxins causes local tissue-change and constitutional influences. The endometrial surface has a diffuse, more or less dry, or less often a purulent fluid or yellowish or yellowish-green covering or coating. In some cases the disease is circumscribed to one portion of the endometrium, particularly the placental site, which is covered by a firmly attached diphtheritic membrane; also the thrombi may be converted into abscesses. Histologically there is seen a necrotic layer of decidual cells containing streptococci, a reaction zone infiltrated with collections of small round cells, but much less extensive than in putrid endometritis. Streptococci in collections or as a single chain are also found in this layer and for some distance in the underlying muscle-tissue. The infection extends through the lymph-channels. In the pyemic form the thrombi are infected, disintegrated, and the infection extends through the venous system.

The *cervical mucosa* may be similarly diseased, either as a diffuse interstitial inflammation with purulent infiltration of the interglandular tissue, or more often as an inflammation of a small laceration. In the first the mucosa is covered with pus, swollen, and intensely reddened; and in the latter the wound is covered with a purofibrinous membrane, from which the infection extends through the lymphatics. The portio vaginalis may be affected in a like manner.

Puerperal metritis also appears in the form of a putrid and a septic inflammation.

Putrid metritis (*metritis putrida*) results from a mixed infection of streptococci and saprophytic micro-organisms. It is not a frequent disease. The tissue destruction is more extensive than in any other puerperal affection. The uterine wall, usually in its entire thickness, is softened through putrefactive disintegration, brownish red in color, or in the more advanced stage green in color, and so soft that it is easily perforated with the finger—putrescent uteri. The putrefactive disintegration may rarely involve only the inner layers of muscle-tissue, being separated from the outer layers by a line of demarcation. The disintegrated tissue here may be separated more or less en masse and discharged—metritis dissecans. Emphysema of the myometrium may occur in this disease. Histologically the disintegrated tissue contains streptococci and the various saprophytic bacteria.

Septic metritis (*metritis septica*), the infection of the myometrium with streptococci, appears as a phlegmonous inflammation. The muscle-wall is soft, doughy but elastic, and on section excessively edematous. Besides

these changes there is a septic lymphangitis or a thrombophlebitis; most frequently a lymphangitis, involving mostly the lateral walls of the uterus, the connective tissue of the cervix, and particularly the muscle-tissue just beneath the peritoneal covering. The lymph-vessels are filled and dilated with pus or purulent material composed of detritus and a few leukocytes. Those just beneath the endometrium contain streptococci and pus. In the myometrium more or less diffusely arranged pinhead to larger cavities (lymph-spaces) are found, containing the puriform material described or pus. In the lymph-vessels the process is found temporarily limited by lymph-thrombi.

The thrombophlebitic form arises in the veins and their contained thrombi at the placental site and extends deeper and deeper, being in each vessel temporarily limited by organized thrombi to the pampiniform plexus of the parametrium and ovarian veins. The thrombi and the intima endothelium are destroyed, and the outer wall of the vein infiltrated. On section many large and small cavities and canals with smooth walls are seen in the myometrium, filled with pus—veins which may be followed to a disintegrated thrombus.

Puerperal perimetritis appears as an exudative inflammation, the infection having extended through the lymph-vessels to, or having involved, the peritoneal covering of the uterus. The peritoneal surface is covered with a fine spider-web-like fibrinous coating, which progressively increases in thickness with the duration of the disease. The coating may have a serogelatinous character or be infiltrated with green purulent masses. Where the course of the inflammation is chronic or subacute, the fibrinous exudate is formed through the organization of adhesions between neighboring organs, such adhesions often containing encapsulated collection of pus. Where the course is acute the infection usually spreads diffusely over the peritoneum, causing general peritonitis. If the patient survives the infection, organized adhesions remain.

Puerperal sepsis has its origin either in a puerperal endometritis or infected laceration wound of the cervix, portio, or vagina. The infection extends from the primary lesion through the lymphatics to the parametrium, causing here a phlegmonous purulent parametritis; from here to the peritoneal cavity, causing a purifibrinous general peritonitis and death. Sometimes the infection extends through the lymph-stomata of the diaphragm, and is followed by a purulent pleuritis. The tubes and ovaries are secondarily infected from the peritoneum or rarely from the uterine cavity. The virulence of the streptococci may be so great and the infection so rapid that the peritoneum is only reddened before death occurs; or, on the other hand, the virulence of the cocci may be so weak or resistance of the body-organism so great that the process is slow, and the patient survives. In the latter instance numerous collections of pus surrounded by peritoneal adhesions are formed.

Puerperal pyemia has its origin in a streptococcic infection of the venous thrombi at the placental site. The infection here spreads through the venous blood-system to the ovarian veins. There is present an intense peri-uterine phlebitis and periphlebitis, the veins being surrounded by new-formed connective tissue with gelatinous infiltration undergoing suppuration. The veins contain pure pus or a brownish slimy mass to a point where there is a limiting thrombus. Infected degenerated thrombi are separated as

emboli and carried to the right heart, lungs, kidneys, brain, liver, or skin, with the formation of embolic infarcts, metastatic abscesses, etc.

Subinvolution of the Decidua.—The normal involution of the decidua into the stroma-cells of the endometrium may be incomplete, microscopic areas composed of groups of decidual cells remaining long after labor or, more frequently, after complete abortion—endometritis post abortum. Collections of distinct, well-formed decidual cells, surrounded by decidual cells undergoing involution and normal stroma-cells, are found in the superficial layers of the endometrium, or decidual cells with large vessels in the neighboring tissue, indicating the decidual character of the cells, are seen in the deeper layers of the endometrium, the immediately underlying muscularis, and often in the adventitia of the arteries. In the remaining mucosa in cases following abortion there is an interstitial or glandular endometritis. The blood-vessels often show hyaline degeneration, and not infrequently the lumen is obliterated. The clinical symptom is hemorrhage. The cause of the subinvolution process is unknown.

Also when chorion villi, even though few in number, are retained attached to the endometrial wall there is always an incomplete involution of the decidua, decidual cells being found with and distant from the more or less changed chorion villi. The endometrium elsewhere is the seat of an interstitial or glandular endometritis, and is infiltrated with numerous hemorrhagic areas. The blood-vessels show hyaline degeneration.

Placental Polypus.—The retention of a portion of the placenta after labor or abortion, with the contraction of the uterine walls, results in the formation of this tissue into a more or less pedunculated polypus. From repeated hemorrhages causing the deposit of fibrin on the surface the polypus progressively increases in size.

Syncytioma malignum (the disease also described as syncytial carcinoma, sarcoma deciduo-chorio-cellulare, deciduoma, deciduosarcoma,

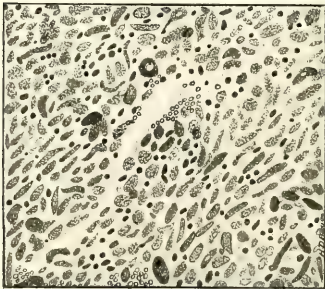


FIG. 343.—Syncytioma malignum.

chorio-epithelioma) is a peculiar new-growth of the uterus occurring after pregnancy, the parenchyma of which is derived from the epithelial cells covering the chorion villi. Syncytioma malignum is characterized from all other new growths in that the parenchyma, at least in a typical case, is derived from two forms of cells, the syncytium and Langhans' layer; that it occurs only after pregnancy; and that its origin is in fetal tissue and its development in the maternal organism. In typical cases the disease immediately follows birth,

abortion, the discharge of a hydatiform mole (18 of 35 cases), or a destroyed extra-uterine pregnancy. In some instances the disease has remained latent for weeks, months, or even a year after pregnancy. It is a highly malignant tumor, growing rapidly, causing profuse hemorrhage and cachexia, and quickly giving metastasis, even to distant organs. The primary position of development is in the chorion frondosum; in that following a hydatiform

mole it may develop from any portion of the inner surface of the uterus to which are attached chorion villi. Further, according to Schmorl, normal or hydrosopic (that of the hydatiform mole) degenerated chorion villi may be separated, carried to distant parts of the body, and there develop as a primary syncytioma malignum, as in the vagina.

The tumor is a nodular or a pedunculated outgrowth attached to the inner uterine wall; a growth extending from the endometrial surface as a fungoid outgrowth, or rarely it is an intramural growth covered with mucosa. The tumor-mass may be the size of a cherry-stone to an apple or much larger. It is composed of a soft, fragile, porous, spongy mass of tissue, light to dark red in color, and infiltrated diffusely with blood or containing circumscribed hemorrhages. The diseased tissue is sharply outlined from the muscular wall, or the limitations of the diseased tissues cannot be determined, the uterine wall being infiltrated to a greater or less extent with small cavities containing tumor-constituents. The metastatic growths are



FIG. 344.—Syncytioma malignum: section from uterine wall; new growth arising from epithelium of villus; wandering syncytial cells in muscularis.

identical in appearance and histologically with the primary growth, and have been found most often in the vaginal walls, frequently in the lungs, and not rarely in the ovaries, spleen, and liver. Metastasis takes place wholly through the blood-vessel system, except, very late in the disease, possibly through the lymphatics.

Histologically the syncytioma malignum arises as a new growth of the syncytium and Langhans' layer of chorial epithelium, the former being thickened and more or less broken through by the Langhans' layer. With further proliferation of these two constituents, other tissue-forms disappearing, a new growth is formed having no tumor-stroma and no blood-vessels. The syncytial elements are seen as large protoplasmic masses, long and irregular in shape, often running in a direction parallel one to the other, in strata. The outer limitation of the cellular mass is marked by a sharp but very fine line, or is seen as a broken edge. At other times the boundary of the mass is not to be distinctly determined, the protoplasm, as though

through destruction, gradually vanishing. The protoplasm is cloudy, appears filled with fine granules, but is otherwise homogeneous, except that it contains nuclei-staining substance. In the protoplasm also are here and there vacuoles, frequently closely associated, which may contain red blood-corpuscles. The nuclei lie regularly in position, may be irregular in form, and strongly imbibe stains.

The elements of Langhans' layer lie closely in contact in groups of varying size. They are irregular-shaped cell-masses, long or spheric, and have a distinct cell-membrane; the protoplasm is pale and translucent, and may contain lacunæ. Nuclear division figures, never found in the syncytial mass, may be discovered here.

These two constituents, as said, alone form the tumor-substance, the growth of the Langhans' cells being broken through by larger or smaller collections of syncytial masses. Sometimes there is a certain regularity of formation, in that the syncytial masses are surrounded by a mantle of the groups of Langhans' cells. In other cases the syncytial masses are in excess, usually found in sections running at right angles to the base of the tumor. Hemorrhagic destruction of the growth or apoplexies are always present to a greater or less extent. Also necrosis occurs. The adventitia of the blood-vessels found toward the base of the tumor may be seen separated from its walls by tumor-cells, and obliterating the lumen of the vessel. Later the endothelial layer is broken through and the vessel filled with and destroyed by the tumor-cells. This character of destruction of blood-vessels explains the hemorrhage and the great tendency to embolic metastasis. The syncytioma malignum may appear also as a simple infiltration and thickening of the uterine wall, of the decidua and myometrium. The tissues are infiltrated with numerous, mostly isolated cell constituents. The differentiation between Langhans' cells and the syncytial masses in this latter form of growth is difficult, since no syncytial strata with the cell-masses running parallel are formed. The uterine wall away from the tumor-growth is covered with decidua, or in part with a normal or inflamed involuted mucosa. In many cases the glands are surrounded by syncytial epithelium.

THE FALLOPIAN TUBE.

Congenital Deformities.—**Complete absence** of both tubes is only observed combined with a complete failure in development of the other genital organs. One tube is absent with the uterus unicornis. The tubes may be found atrophied, converted into a connective-tissue cord, or have entirely disappeared, mostly with rudimentary formation of the uterine cornu. Atrophy of the muscular wall and mucosa in the middle or outer two-thirds of the tube, leaving the peritoneal covering intact, has been observed. Accessory tube ostii with fimbria, one to five in number, are found in from 9 to 16 per cent. of normal tubes. Accessory rudimentary tube-like formations with or without a lumen, attached to or near the normal tube, but mostly not communicating with the tube, are not infrequent. They have fimbria or are formed into a small cyst, vary in number and length, and may rarely be the size of a normal tube. Diverticula of the mucous membrane in the wall of the tube occur (Landau). An accessory well-formed tube on one side, with or without an accessory ovary, has been described.

A congenital excessive spiral folding of the tube may occur; also an abnormally long or short tube.

Abnormal positions of the tube, as a rule, occur with a malformed uterus or prolapsed ovary. The tube may be contained in the sac of an inguinal or femoral hernia.

Acquired displacements of the tube are common with inflammatory disease, ovarian and uterine tumors, displacements of the uterus, inversion and torsion of the uterus. Torsion or twisting of the tube may occur with ovarian tumors, hydrosalpinx, tubal pregnancy, etc.

Circulatory Changes.—Hyperemia of the Fallopian tube is found as part of a general venous stasis in heart, lung, and liver disease, and in the acute infectious fevers. Disturbance of the circulation with extreme hyperemia takes place in torsion of the tube, strangulation of the tube in a

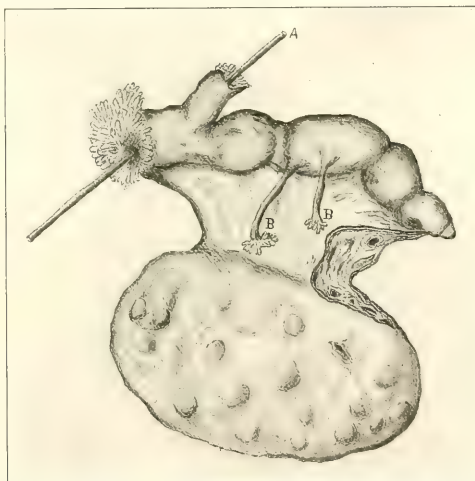


FIG. 345.—Fallopian tube and ovary : A, accessory tubal end with an ostium; B, pedunculated tuft of fimbriae.

hernia-sac, with complete inversion of the uterus, and sometimes from peritoneal adhesions. In the milder grades of hyperemia the tube is thickened, dark red or blue red in color, and the fimbriae are swollen and injected. In the extreme degree hemorrhages are found in the mucosa or muscularis (apoplexies), blood collects in the lumen, and finally hyaline degeneration and necrosis may result. Hemorrhage from the abdominal ostium may cause the formation of a peritubal hematocoele. Hemorrhages into the tube-wall are also found in hemophilia, purpura hæmorrhagica, phosphorus and other poisoning, extensive burns, and as a postmortem hemorrhage.

Hematosalpinx, the collection of blood in the lumen and distention of the tube after closure of the abdominal ostium and closure or obstruction of the uterine ostium, is found with hematocolpos, hematometra, tubal pregnancy, hemorrhage or thrombosis of the tube-wall, through the expression

of blood from the uterus during menstruation, and rarely from torsion of the tube. Such a distended tube may reach the size of a child's head. The collection of blood is a tar-like, chocolate-colored mass, and, except in that of tubal pregnancy, containing no clots. In the early stages of development the tube is thickened through hyperemia, and with increase of the blood collection, through pressure, the walls become thin and atrophied. The epithelium may in the beginning be intact, but with thinning of the wall both the epithelium and the mucosa are destroyed. The walls contain blood-elements and pigment, free or in the cells, and a not inconsiderable amount of small round-cell infiltration is seen surrounding dilated blood-vessels. Irritation from the blood-mass, and sometimes escape of blood from the abdominal ostium, causes the formation of peritoneal adhesions to surrounding organs and thickening of the peritoneal wall. Such adhesions to intestines may result in infection and suppuration of a hematosalpinx.

Inflammation (*salpingitis*) of the Fallopian tube is nearly always caused by bacterial infection, the most frequent and important of which are gonorrheal and puerperal infections. The infection usually extends directly from the uterus, occasionally from the peritoneal cavity, from hollow viscera or tumors containing bacteria, through the lymph-channels (pelvic connective tissue), and probably very rarely through the blood-vessels. Very rarely mechanical (massage, vaginal examination, and operative injury), chemical (chemical fluids introduced through the uterine cavity), and thermic (catching cold) irritations have been the cause of catarrhal salpingitis; also such an inflammation may occur during the course of the infectious fevers. Abnormal tortuosity of the tube and retrodisplacement of the uterus are predisposing causes. The infecting bacteria are the gonococcus, streptococcus, and staphylococci, and in isolated cases the pneumococcus, *Bacterium coli commune*, stralen pilz, *Diplococcus albus*, saprophytes, and various other organisms have been found.

The degree of pathologic change taking place in the tube varies very much. No classification is determinable from the etiology of inflammation. Commonly all three walls of the tube are involved. In rare cases the inflammation is chiefly localized to the mucosa—endosalpingitis—as a catarrhal or purulent inflammation. In the catarrhal form the tube is seen slightly thickened, abnormally tortuous and reddened, particularly at the fimbriated extremity. The mucosa is swollen, injected, and covered with a cloudy-white catarrhal secretion. Histologically the mucosa is infiltrated with leukocytes, the blood-vessels are dilated, and here and there are seen minute areas of small round-cell infiltration. Sometimes also small hemorrhages are found. The cylindric epithelium is intact and normal, or shows cloudy swelling and fatty change. In chronic cases the surface epithelium may be atrophied in places, the mucous membrane rugæ adherent one to the other, causing partial obliteration of the lumen and the formation of small cysts—pseudofollicular salpingitis. Ulcerations of the mucosa and a perforating ulcer in catarrhal inflammation are reported. In the purulent form the hyperemia and small round-cell infiltration are much more pronounced, and more or less destruction of, particularly the surface, epithelium takes place. In some instances the mucosa becomes necrotic. The secretion is purulent.

The inflammation not infrequently extends to and chiefly involves the muscular wall—mesosalpingitis, interstitial salpingitis, myosalpingitis. The

tube is much thickened, abnormally tortuous, the mucosa swollen, and the lumen stenosed. Histologically the muscularis is diffusely or linearly infiltrated with small round cells and thickened through muscular hypertrophy, and chiefly through hyperplasia of the connective tissue. The cylindric epithelium of the mucosa may be destroyed, and the inner surface of the tube covered with granulation-tissue. Adhesions between rugæ may be present. Rarely small abscesses are found in the tube-wall—disseminated interstitial salpingitis. An increased peristaltic movement of the tube to cause the discharge of materials from its lumen in catarrhal inflam-



FIG. 346.—Acute septic salpingitis: section about the middle of the tube.

mation is thought to be partially the etiology of the more pronounced change in the muscularis. By extension of the inflammation to the peritoneal surface—perisalpingitis—pelvic peritoneum, and surface of the ovary a yellowish fibrinous or purulent exudate, and with organization more or less extensive adhesions to neighboring organs and structures, are found with various displacement of the tube.

Through adhesion of the fimbriated extremity to other organs or structure, or inversion of the fimbria into the lumen of the tube and adhesion of the peritoneal surfaces of the fimbria, the abdominal ostium is partially or

completely closed. Also the lumen of the uterine end of the tube becomes closed or stenosed through swelling and adhesion of the mucosa. When such a closed tube is filled with purulent material the condition is known as **pyosalpinx**. Such a cystic distention of the tube varies in size from the thickness of a little finger to a hen's egg; rarely it reaches the size of a fetal head. The tube is tortuous and often folded upon itself. The peritoneal surface is injected, covered with fibrinous or purulent exudate, and later with organized connective tissue and adhesions. The muscular wall is thickened as in mesosalpingitis, edematous, with the lymph-spaces dilated and filled with pus-cells, the blood-vessels dilated, and there is a diffuse or linear small round-cell infiltration. The thickening is chiefly a hyperplasia of connective tissue. In rare, long-standing pyosalpinx the muscle-wall is thinned. The mucosa may be completely destroyed, and the inner surface of the tube covered with granulation-tissue or an abscess-membrane. In other cases the mucosa remains more or less intact, also the cylindric epithelial cells, even to the preservation of their cilia, but the stroma of the mucosa is swollen and infiltrated with small round cells. The contents of the tube is a purulent, mucopurulent, or caseous material. Bacteria are found in the pus in very acute pyosalpinx only rarely, having been destroyed by their own toxin products. Abscesses may form in the adventitious tissue outside the tube—perisalpingitic abscess. A pyosalpinx may rupture into the abdominal cavity, or through adhesion to intestines, bladder, vagina, or abdominal wall, with thinning of the intervening walls, into these organs, or externally with the formation of a fistula.

Hydrosalpinx is the cystic distention of the tube with a serous fluid where the abdominal and uterine ostia are closed, or the abdominal ostium alone is closed and the uterine ostium stenosed. It is thought to follow a catarrhal salpingitis, perisalpingitis, and pelvic peritonitis, or a chronic pyosalpinx becomes a hydrosalpinx. The closure of the tube ostia with a functioning mucosa caused the collection of secretions, and thus the distention of the tube. Also the fluid contents of a hydrosalpinx is to a very great extent a serous exudate from the blood. The tube is tortuous, often folded upon itself, and more or less covered with adhesions. It varies in size from a lead-pencil to a fetal head. The dilatation of the walls is usually most pronounced in the outer two-thirds, the tube frequently being retort-shaped. The walls are of varying thickness, in the larger as thin as paper. Histologically, in the early stages the walls show the pathologic changes of a catarrhal salpingitis; later the pressure of the fluid within the tube causes the mucosa and muscularis to atrophy and become thinned out. The wall is then composed entirely of connective tissue, or a few longitudinal muscle-fibers also remain. Sometimes a slight, small round-cell infiltration is seen in the muscularis. The epithelium of the mucosa, deprived of its cilia, may remain intact for a long time, then from pressure be flattened, and finally destroyed. The fluid contents is clear, cloudy, or slightly bloody. Microscopically they contain leukocytes, separated degenerated epithelium, and blood-cells. Absorption of the fluid contents may take place, the abdominal ostium remaining closed. A calcareous incrustation of the inner surface may occur. Through infection from an intestine a hydrosalpinx may be converted into a pyosalpinx. Where the uterine ostium remains open, periodical discharges of the fluid contents into the uterine cavity sometimes

take place—hydrops tubæ profluens. There may be a follicular distention of the tube—hydrosalpinx follicularis.

Tubo-ovarian cyst, a communication between the tube and a cyst of the ovary. The fimbriated end of the tube is often seen spread out on the inner surface of the cyst. The fluid contents are similar to those of the hydrosalpinx. The mode of formation of the tubo-ovarian cyst is not definitely known, but it is thought to be produced by absorption of the wall between a hydrosalpinx and a follicular cyst of the ovary, a pyosalpinx and an ovarian abscess, the tube and an inflamed ovarian cyst, through adhesion of the tubal abdominal ostium to an ovarian follicle, or (Bland Sutton) it is due to the presence of a tunic of peritoneum which occasionally invests the normal ovary in the same way the funicular pouch clothes the testicle—ovarian hydrocele.

Salpingitis nodosa isthmica, a nodular inflammatory thickening of the uterine end or the isthmus of the tube, is usually caused by gonorrheal infection. The nodules vary in size from that of a pea to that of a bean, one or more being found together. There is a localized hypertrophy and hyperplasia of the muscular wall, particularly the circular fibers. Sometimes the mucosa shows cicatrices. Small round-cell infiltration is rare. The tube, as a rule, shows other indications of inflammation. In other instances it would appear that a portion of the mucosa is infolded, a cyst being formed, surrounded by a hypertrophied and hyperplastic muscularis—salpingitis isthmica nodosa cystica. It is also thought that the disease may arise in an intraperitoneal accessory tube, in the remains of the Wolffian duct, or as a hyperplasia of the peritoneal endothelium.

Tuberculosis of both tubes, or rarely, of one tube, is found in the child and adult. The tube is the most frequent site of tuberculosis in the female genital tract, usually occurring as a secondary, but often as a primary tuberculosis. The pathology of the tubercular process here does not differ from that of the mucous membranes in other parts of the body, as the ureter. It occurs as an acute diffuse tuberculosis, characterized by rapid caseation and liquefaction necrosis of the mucosa and part or all of the muscular wall; a chronic diffuse tuberculosis, with the same changes as the former, but slow in progress; a chronic miliary tuberculosis, localized to the mucosa; and a chronic fibroid tuberculosis, where there is the formation of fibrous connective tissue, little or no caseation necrosis, and perhaps calcareous infiltration. The tube-lumen contains mucus, more often purulent or caseous material, and rarely calcification plates. Tubercle bacilli are found in considerable numbers in the tube-contents, with more difficulty in the mucosa and muscularis. The ostia of the tube are often closed, forming a tubercular pyosalpinx, which may reach the size of a child's head. The endometrium and ovary are often secondarily infected from the tube; rarely the intestines, rectum, and vermiform appendix; also a general tuberculosis may result. Tuberculosis of the tube is often the primary origin of a tubercular peritonitis; likewise the tube is sometimes infected from a tubercular peritonitis. A mixed tubercular and gonorrheal infection of the tube has been described.

Syphilis (*syphilitic salpingitis*) of the tube has very rarely been found in the syphilitic newborn infant, child, and adult. The tube is enlarged, tortuous, inflamed, the lumen usually obliterated, and the muscularis infiltrated with masses of small round cells—miliary gummas.

Actinomycosis, as a secondary infection from the peritoneum, is reported in 2 cases.

New Growths.—Cystic Tumors.—The hydatid of Morgagni, the occlusion and dilatation of the outer end of the duct of Müller, is a very common physiologic cystoma found growing in relation with mostly the fimbria of the tube. Serous and lymphatic cystomata of varying size are found beneath the peritoneum of the tube and mesosalpinx. A dermoid cystoma of the tube-wall is reported. Polypoid growths, arising from decidual tissue in tubal pregnancy, are very rarely observed. Papillomata of the mucosa are rarely found growing in and filling the tube-lumen where a previous chronic inflammation of the tube has been present. By adhesion of the papillæ small cysts are formed—papilloma cystica. The pelvic peritoneum may be secondarily infected with such papillary growths. Papilloma of the tube may be associated with papilloma of the ovary. In such cases, if the tubal abdominal ostium remains open there is an associated ascites.

Fibroma, myoma, and fibromyoxoma, as small nodular tumors of the muscularis, are extremely rare. **Lipomata**, as a collection of fat-tissue between the layers of the mesosalpinx in relation with the tube, are not infrequent.

Five cases of **sarcoma**, 4 arising in the mucosa and 1 in the muscularis, have been described. Those of the mucosa were small round- or spindle-cell sarcomata appearing as a fungoid, polypoid, or nodular tumor; that of the muscularis was a myxosarcoma. It is possible that these sarcomata were a form of carcinoma.

Carcinoma, as a primary growth of the mucosa, may appear as a malignant adenoma or adenocarcinoma having the type of the malignant adenoma and adenocarcinoma of the body of the uterus. It is mostly a unilateral growth. Secondary carcinoma extends from the uterus, ovaries, or peritoneum.

A secondary **syncytioma malignum** of the tube may occur.

Parasites.—Echinococci, as a secondary infection, are very rarely found in the tube.

THE ROUND LIGAMENT.

The canal of Nuck may persist to the labium majorum and become the sac of an ovarian hernia. Hemorrhage into the substance and a suppurating hematoma of the intrapelvic portion of the round ligament have been observed. Inflammation is very rare, and is, as a rule, the extension of a puerperal thrombophlebotatic process. Adenomyoma of the intrapelvic portion, having the form and genesis of adenomyoma of the uterus, are described; also fibroma, myoma, and fibrolipoma. The canal of Nuck may be distended with serous fluid (hydrocele), forming a cystic tumor in relation with the round ligament. A cystic tumor in the substance of the ligament has been found, which has the same genesis as adenomyoma. Such cystomata develop in the inguinal canal, inguinal region beneath Poupart's ligament, or in a labium majorum.

EXTRA-UTERINE PREGNANCY.

By extra-uterine pregnancy we understand the arrest and development of the fertilized ovum in the ovary—ovarian pregnancy—or in any portion of the Fallopian tube, from the fimbriated extremity to the interstitial portion inclusive—tubal pregnancy.

The etiology is obscure. Tubal pregnancy is believed to be due to some condition or disease of the tube or ovary which interferes with or obstructs the normal downward progress of the fertilized ovum from the Graafian follicle to the uterine cavity. Such conditions or disease are obstacles within the lumen, by which its caliber is diminished—polypi; diseases of the tube-walls and peculiarities of its anatomy or form—catarrhal and purulent salpingitis, torsion of the tube, diverticula from the lumen of the tube, persistence of the fetal type of the tube, etc.; and disease, abnormal, multiple fertilization or oversize of the ovum. Very frequently there is no demonstrable anatomic cause.

Any portion of the tube may be the seat of pregnancy. When the fertilized ovum is implanted in the interstitial, intermural portion of the tube, it is designated as interstitial pregnancy; in the intraligamentary or tube proper portion of the tube, as ampullar and isthmal pregnancy; and in the fimbriated extremity, as infundibular pregnancy. When such a pregnancy remains and develops in its original position, it is designated as primary extra-uterine pregnancy; upon changing its position by rupture or further development, it is designated as secondary interstitial pregnancy. The development of the ovum in that portion of the tube surrounded by uterine muscle is of comparatively rare occurrence. The ovum commonly develops toward the uterus. In the early stages of gestation there is an associated symmetric enlargement of the uterus; later, an asymmetric enlargement of the portion in relation with the pregnancy. In the course of gestation the ovum and its membranes may be partially or completely extruded into the uterine cavity—tubo-uterine or secondary uterine pregnancy.

Ampullar and isthmal pregnancy are the most frequent forms of extra-uterine pregnancy. Commonly the ovum is implanted in the outer half of the tube—ampullar pregnancy; less frequently in the inner, toward the uterine end of the tube—isthmal pregnancy. Early the pregnancy is seen as a spindle-form; later, as an ovoid swelling, usually covered with adhesions, which attach it to the surrounding structures. The growth of the ovum is, as a rule, toward that portion of the tube covered with peritoneum; less often it separates the layers of the broad ligament—secondary intraligamentary pregnancy. The approximal portion of the tube may form a pedicle, and torsion of the pedicle take place.

Infundibular Pregnancy.—In this variety the ovum is in part surrounded by the tube-wall and fimbria, and a zone of the periphery extends into the abdominal cavity. When the greater part of the ovum is extruded into the abdominal cavity, it is designated as secondary tubo-abdominal pregnancy. The placenta is attached to the tubal mucous membrane. Tubo-ovarian pregnancy is a rare form of extra-uterine pregnancy, in which the ovum is partially surrounded by the tube-wall and by a segment of ovarian parenchymatous tissue. It is commonly believed that the ovum here develops in the so-called ovarian tube—that is, a tube whose fimbriated extremity is found glued down by adhesions to a limited portion of the ovary. It is possible, however, that such pregnancies are primarily ovarian, and only after rupture do they become adherent to and surrounded by the fimbriated extremity of the tube (Gebhard).

Ovarian pregnancy, the implantation and development of the fertilized ovum in the Graafian follicle, is a rare occurrence. Its etiology is thought to be a disturbance of the normal ovulation process, in which the

ovum fails to leave the open follicle, and is here fertilized. After fertilization the wound in the follicle closes and the gestation continues as in the tube—ovarian follicular pregnancy; or, less frequently, the follicle remains open, the ovum receives its nourishment from the follicular membrane, and also, after extending beyond the limits of the follicle, from the surrounding peritoneum. The extrusion of the ovum into the abdominal cavity is sometimes so pronounced that it has been described as ovario-abdominal pregnancy. In ovarian pregnancy the gestation sac is found surrounded partially or completely with ovarian parenchymatous tissue, and the correlated tube is normal, or it must be proved not to be the primary position of implantation of the ovum.

With all extra-uterine pregnancies there is a relative degree of hypertrophy of the uterus, and a decidua forms from the corporeal endometrium which has the character of the decidua vera. The decidual membrane separates *en masse* or piecemeal, and is thrown off after death of the embryo or during its normal development (eighth to tenth week). The decidua again forms only when the gestation continues undisturbed. The fetal membranes in extra-uterine pregnancy are identical with those of intra-uterine pregnancy. The maternal membranes differ in that they are much thinner and less extensive. The tubal mucous membrane shows a distinct formation of decidua, but only immediately surrounding the ovum. Beyond this to either side the epithelial cells are ciliated and normal. The surface of the decidua is irregular, having furrows and elevations many millimeters in thickness. Sometimes the mucous membrane rugæ are seen beneath the decidua. The decidual cells in extra-uterine pregnancy develop from the tubal mucous membrane stroma—according to Zedel, from the perivascular portion of the stroma; in ovarian pregnancy from the tunica propria. The decidua reflexa is not always demonstrable.

In the early stages of pregnancy the tube-wall is considerably thickened through hypertrophy and hyperplasia of its muscular elements; but as pregnancy advances this active compensatory hypertrophy is overcome by the pressure of the growing ovum, and more or less dilatation and thinning of the tube-wall result. The spindle ends of the swelling are thickened and the intervening wall dilated. Sometimes one portion of the wall of the gestation sac is thickened and another dilated—atrophied—so that none of the tubal muscle-fibers remain. In rare cases the hypertrophy persists in an advanced stage of the pregnancy.

Peritoneal adhesions usually surround the tube. They are in part at least due to reactive irritation from the growing ovum, and have nothing to do with the etiology. Also the endothelium of the tubal serosa is found proliferated; a desquamation of the endothelium rich in protoplasm. The growth of endothelium is often circumscribed, and may form polypoid or filamentous outgrowths.

In extra-uterine pregnancy the course of gestation is usually disturbed between the first and fifth months, and the ovum destroyed. Hemorrhage takes place beneath the placental site or between the fetal and maternal membranes, and the embryo dies. At this time also the dilated tube-wall often ruptures, commonly at or near the site of placental insertion, with profuse hemorrhage into the peritoneal cavity, or, rarely, between the layers of the broad ligament. An ampullary or infundibular pregnancy is frequently discharged from the abdominal ostium without rupture of the

tube-wall—tubal abortion. In rupture or tubal abortion the embryo is discharged alone or with its membranes. The placenta may remain attached and gestation continue where the rupture has taken place between the layers of the broad ligament, or following tubal abortion—secondary abdominal pregnancy. In a similar manner the ovum has been discharged into a tubo-ovarian cyst—secondary ovarian pregnancy.

In rare cases the gestation has continued undisturbed in the tube for eight, nine, or even twelve months, and been removed by celiotomy, or after death remain encapsulated in the peritoneal cavity for years. A viable fetus has been removed by celiotomy in 77 cases (Harris). Very rarely an interstitial pregnancy becomes uterine, and is discharged through the uterus.

The hemorrhage from rupture or tubal abortion results in the death of the patient, the peritoneal cavity being found filled with free blood; or the patient survives, and a retro-, para-, or supra-uterine hematocele is formed,



FIG. 347.—Ruptured (eighth week) extra-uterine pregnancy; ampullar tubal pregnancy. The fetus and its membranes were extruded intact. Specimen removed by operation.

or a hematoma between the layers of the broad ligament. All such hematoceles are primarily peritubal, the blood following the course of the tube into Douglas' cul-de-sac, thus forming a retro-uterine hematocele. Where the cul-de-sac is already occupied by a tumor, the hematocele is developed para- or supra-uterine (Sänger). Such hematoceles are further diffuse or localized; the former arise from profuse and rapid hemorrhage into a previously formed network of connective tissue, and the latter from slow hemorrhage. In the localized or solitary hematocele the clotting takes place from without inward, forming an ovoid tumor composed of a soft brown mass of changed blood surrounded by a fibrin capsule. More or less irritation and low-grade inflammation follow, causing the development of connective-tissue adhesions to the surrounding pelvic and abdominal organs. The hematocele is either finally absorbed, the capsule-walls falling together, or a secondary serous change takes place, with the formation of a serous cyst.

The embryo and its membranes, after death in the early stages of devel-

opment, if not removed by operation, are absorbed. Later, well-formed fetuses may remain encapsulated with connective tissue in the abdominal cavity for years, retaining more or less their form, mummification or lithopedian change taking place, or maceration of the fetus occurs, leaving the bony structures. The bones of a macerated fetus may ulcerate into a hollow viscus and be discharged.

Placental polypi may develop from chorion villi retained in the gestation sac; also the syncytioma malignum.

Suppuration and putrefaction of an extra-uterine pregnancy or hematocele occur as in an ovarian tumor.

THE OVARY.

Congenital Deformities.—Complete absence of both ovaries occurs only with agenesis of the other genital organs—the uterus and vagina. One ovary is absent only with a rudimentary development of one side of the genital tract, as in uterus unicornis. Undeveloped ovaries, rudimentary ovaries, or hypoplasia of the ovaries are found with the uterus infantilis, uterus fetalis, or atrophied uterus, in cretinism and chlorosis. Such undeveloped ovaries usually have few primordial follicles, and are mostly composed of connective tissue.

An accessory ovary or ovaries have not been authentically observed; those described are believed to be acquired anomalies.

Displacement of the Ovary.—The ovary is variously displaced by new growths of the uterus and inflammatory disease of the tube. It is prolapsed into Douglas' cul-de-sac or to a less degree (usually the left ovary) through changes which increase its weight, as hyperemia, hypertrophy, edema, cystic formation, inflammation, or adhesion. Also it is prolapsed with retroversion and prolapse of the uterus. The prolapsed ovary is swollen and hyperemic, either primarily or secondarily, through venous stasis.

The ovary may be found in the sac of an inguinal or femoral hernia—ovariocele. Very rarely it has been found displaced through the ischiatic foramen, obturator foramen, or umbilicus. The inguinal or femoral ovariocele is most often a congenital bilateral, irreducible deformity, frequently complicated with an undeveloped uterus, uterus bicornis, uterus bipartitus, or pseudohermaphroditism. The acquired inguinal or femoral ovariocele is, as a rule, unilateral and reducible, and the sac contains also the tube, omentum, or intestines. Through injury and disturbance of the circulation hemorrhage takes place in the stroma of the ovary, and blood-cysts are formed. Also cystic degeneration and suppuration of the ovary may occur.

Hyperemia of the Ovary.—Hyperemia of the ovaries occurs with a general venous stasis of the genital system, or the hyperemia may be localized to the ovary. A physiologic hyperemia is present with ovulation and menstruation and during pregnancy, causing in the latter enlargement of the organ through cellular hyperplasia and serous infiltration. Pathologically hyperemia is found with myomata and malignant new growths of the ovary, and in the prolapsed ovary. Such an ovary is usually enlarged, edematous, and soft in consistency. An intense hyperemia occurs with torsion of the ovarian pedicle. Where the pathologic hyperemia is of long duration, changes take place in the parenchyma and stroma-tissue

which are quite identical with those of noninfectious chronic oöphoritis. A phlebectasis of the medullary veins is described by Kaufmann; also an angiodystrophy by Bulius and Kretschmar. In many cases of puerperal osteomalacia there are found a marked increase and hyaline degeneration of the blood-vessels, with an acceleration of the ripening of the follicles.

Hemorrhage into the ovarian stroma-tissue results from hyperemia; in that of excessive physiologic congestion, from injury or compression of the ovarian veins, torsion of the ovarian pedicle, or it is produced through direct injury. Also hemorrhage into the ovary may occur during the course of the infectious diseases, scorbutus, tuberculosis, cerebral apoplexy, and heart-failure. It appears as a circumscribed or diffuse hemorrhagic infiltration of the stroma; or as a hemorrhage localized to the Graafian follicles. The circumscribed hemorrhage of the stroma commonly occurs about a follicle, and is caused by the rupture of an overfilled thin-walled blood-vessel—ovarian apoplexy. Such hemorrhage may infiltrate to a greater or less extent the neighboring tissue, and confuse with smaller hemorrhages. Much more rarely a diffuse hemorrhagic infiltration of the ovary is found, the organ being much enlarged and of the consistency of a sponge or the spleen—ovarian hematoma. The hemorrhage into a Graafian follicle forms a hemorrhagic cyst, which sometimes reaches the size of a walnut. The blood contained in such a cyst is tar-like, later becoming an ochre-yellow homogeneous mass. The follicle of a healthy ovary may be found filled with a serosanguinous fluid, probably from diapedesis. A congenital hematoma of the ovary is described.

Hypertrophy of the Ovary.—The ovary may be abnormally large, measuring 6 to 8 cm. in length, with a relative increase in the number of follicles. In childhood the ovary may be prematurely developed, causing precocious, early ripening of the follicles, ovulation, and menstruation. In the adult hypertrophy results from increased nourishment to the ovarian tissue, as in disturbances of the circulation and inflammation.

Atrophy of the Ovary.—Atrophy of the ovary is found as a physiologic involution at the climacteric. Pathologically atrophy results from the contact compression of tumors, varicose change in the vessels of the mesosalpinx, and it follows chronic or severe inflammation and hemorrhagic affections. Rare causes of atrophy are phosphorus, arsenic, and opium poisoning, diabetes, profound anemias, phthisis, myxedema, Basedow's disease, and acromegalia. A compression atrophy may be so great that no ovarian tissue is to be discovered. The atrophied ovary is commonly a white, hard body, about the size of a small almond, with the surface smooth, scarred, or deeply furrowed. The white appearance results from extensive thickening of the albuginea. The parenchyma contains no or relatively few follicles; or the follicles are found mostly converted into cysts. The lumen of the blood-vessels is obliterated and the walls show hyaline degeneration. A congenital atrophy of the parenchyma of the ovary has been observed by Pfannenstiel.

Necrosis of the ovary has been observed with severe wound infection and from complete obstruction of the blood-vessel supply in torsion of the pedicle of an ovarian tumor. Also both ovaries were found necrotic in a patient dying with diabetic coma (Israel). The ovary is enlarged, its surface smooth and of a dull-gray color. The ovarian tissue is converted into a ropy fluid detritus or into a drier crumbling mass.

Inflammation.—**Acute oöphoritis** is caused by invasion of the tissues of the ovary with pathogenic bacteria, or it is due to metallic or bacterial intoxication. It occurs with wound infection, gonorrhea, the acute exanthemata, cholera, typhoid fever, pneumonia, influenza, possibly dysentery and pernicious malaria. The *Streptococcus pyogenes*, *Bacterium coli commune*, anaërobic saprophytes, the *Pneumococcus lanceolatus*, typhoid bacillus, and gonococcus of Neisser have been demonstrated as infecting micro-organisms. In many of the cases it is believed that the inflammation results from bacterial intoxication without actual infection of the ovarian tissue.

Infectious oöphoritis is found as an associated inflammation of the stroma, parenchyma, and peri-oöphoronic tissue. It has mostly been observed as a secondary streptococcal infection from the uterus, following labor or operative procedure. Rarely it has appeared as a metastatic infection in severe forms of measles, scarlet fever, and diphtheria. The infection extends through the uterus and Fallopian tube; or through the vagina, uterine wall, and parametrium to the hilus of the ovary by way of the lymphatics, rarely by way of the blood-vessels. The ovary is greatly swollen, hyperemic, infiltrated with serous fluid—serous oöphoritis—or blood—hemorrhagic oöphoritis. The ovary and surrounding pelvic peritoneum are covered either with a fibrinopurulent exudate or pseudomembrane. The liquor folliculi is cloudy. Histologically the germinal epithelium is destroyed by fatty degeneration, the follicle epithelium separated, and the ovum destroyed. An infiltration of leukocytes is seen along the course of blood-vessels and surrounding follicles. The inflammation may progress to the formation of interstitial and follicular abscesses—acute purulent oöphoritis—which through confluence may form a larger abscess or abscesses. As in the uterus and parametrium, there occurs a diffuse phlegmonous, a lymphatic, and a thrombophlebitic form of extension of the inflammation. With extensive blood extravasation in a very acute inflammation, a hemorrhagic necrosis of the entire organ may take place—putrescent ovary.

Where the inflammatory process and infection do not cause death, an ovarian abscess is formed, surrounded by granulation membrane and connective tissue, the ovary is converted into a mass of cicatricial tissue covered with adhesions, or there remains a chronic inflammation with hypertrophy of the ovary.

The infection of the ovary with *Bacterium coli commune* from the intestine or during puerperal fever has appeared as a cyst, follicular abscesses, or as an infection of an ovarian tumor; anaërobic saprophytic infection, as a putrescent oöphoritis; the pneumococcal infection, as multiple infiltrations and abscesses; and that of the typhoid bacillus, as an infection of an ovarian cystoma.

Gonorrheal oöphoritis is rarely found as an extension of a gonorrheal infection by contiguity from the Fallopian tube; more rarely, in cases of severe infection, as puerperal gonorrhea, it is believed the infection extends from the uterus and broad ligament through the lymphatics to the hilus of the ovary.

Acute gonorrheal oöphoritis appears in the form of a purulent inflammation. The germinal epithelium and stroma-tissue commonly show little pathologic change. Isolated small and large follicles, some dilated, and corpus lutei are found filled with pus. The abscess formation is localized to the follicle or corpus luteum wall—pseudo-abscess. At other times the

purulent inflammation extends to the stroma-tissue surrounding the follicles. An acute interstitial inflammation of the stroma-tissue, aside from the abscess formation, has been observed. The stroma-tissue is then infiltrated with small round cells, is edematous, and the blood-vessels are dilated. A gonorrheal tubo-ovarian abscess, formed as previously described, may be present. Gonococci are found in the pus of an ovarian abscess only in very acute infections.

The acute oöphoritis of the infectious diseases and toxic oöphoritis appear as a parenchymatous inflammation. The epithelium of the membrana granulosa shows cloudy swelling and fatty degeneration, the liquor folliculi is cloudy, and the ovum destroyed. A perifollicular blood extravasation is found, particularly in cholera. The inflamed follicles are permanently destroyed, otherwise the ovary returns to normal. In other instances, through metastatic infection of the micro-organism of the special disease, abscesses are formed. Such abscesses may thus be found in the virgin—the post-typhoid ovarian abscess.

Peri-oöphoritis occurs as a fibrinopurulent, pseudomembranous, or adhesive inflammation in acute oöphoritis.

Chronic Oöphoritis occurs as an interstitial and parenchymatous hypertrophy and hyperplasia of the ovary, mostly resulting from long-standing and frequently recurring venous stasis. Such hyperemia, producing chronic oöphoritis, may be due to excessive sexual irritation, subinvolution and displacement of the ovary, myomata and malignant new growths of the uterus, chronic heart and liver disease, and alcoholism.

The ovary is enlarged, about normal in shape; the surface smooth, bossed, or covered with adhesions; and its consistency distinctly increased. The germinal epithelium is usually unchanged. The albuginea is markedly thickened through connective-tissue hyperplasia. The underlying connective-tissue stroma of the parenchyma zone is thicker and richer in cells than that of the normal ovary, but no cellular infiltration is demonstrable. The primordial follicles in a young woman are usually undeveloped, sometimes completely absent. The Graafian follicles are prematurely developed or enlarged, and apparently increased in number. Recent corpus lutei are rarely seen, but corpora fibrosa are frequent. The structure of the follicle is normal, with an intact membrana granulosa; at other times when the disease is of long standing, the membrana granulosa is separated, mixed with the follicular contents, and the ovum destroyed. Later, with absorption of the liquor folliculi, a corpora fibrosa is formed. The tissues of the hilus of the ovary often also undergo hypertrophy. The media, and particularly the intima, of the blood-vessels are thickened, show hyaline degeneration, and are converted more or less into a homogeneous mass containing no or few nuclei. An arteritis obliterans may be present. Through atresia of the follicles the ovarian parenchyma disappears and the stroma-tissue is relatively increased—cirrhosis of the ovary. Under the influence of a persistent chronic hyperemia transudation continues to take place in the sterile follicle, resulting in the formation of the follicular cyst.

Tuberculosis of the ovary is found as a secondary infection from the peritoneum or Fallopian tube, very rarely as a primary disease. Usually both ovaries are affected. It appears in the form of a diffuse miliary tuberculosis, a chronic diffuse tuberculosis with caseation, and as a tubercular abscess. These forms may be combined in the same ovary.

The specific tubercular changes are seen in the stroma of the cortical and medullary substance, either isolated or in relation with the peri-oöphoronic zone. The chronic diffuse tuberculosis develops from the miliary form through confluence of tubercles and caseation, often, when the disease is far advanced, converting the ovary into a large sac filled with dry, crumbling caseous material. The tubercular abscess forms in a follicle—follicular abscess—or as a true abscess in the stroma-tissue. Such an abscess may communicate with a pyosalpinx—tubercular tubo-ovarian abscess. A follicular tuberculosis is described by Schotlander in which there are a marked absence of primordial follicles and decided destructive changes in the larger, and particularly the largest follicles. Rarely a tubercular infection of an ovarian tumor, mostly a glandular cystoma, has been described.

The ovary is sometimes found covered with numerous disseminated nodules, or with fibrinous or connective-tissue thickenings containing the characteristic tubercles—tubercular peri-oöphoritis.

Tubercle bacilli are found in ovarian tissue with great difficulty, only after a long search.

Actinomycosis of the ovaries is extremely rare, and has been observed only as a secondary infection. The stroma-tissue is infiltrated with small punctiform abscesses containing actinomycetes.

Foreign Bodies.—Needles have been found perforating the ovary, entering through the uterus or intestine.

Echinococcic cystomata of the ovary are very rare, and occur only as secondary infections. In two cases (Schultz and Pean) the infection was possibly primary.

Nonproliferating New Growths of the Ovary.—**Follicular cystomata** (*hydrops follicularis*) are retention cystomata of the ripened Graafian follicles. The conditions under which the follicular cystomata of the ovary are formed are not definitely known. It is probable that the follicles are prevented from rupture by an abnormally resisting theca follicularis and thickening of albuginea, resulting in retention of the liquor folliculi and hypertrophy of the follicle. The membrana granulosa undergoes fatty degeneration, the ovum is destroyed, and from hyperemia of the theca interna a transudation of serum takes place into the follicular cavity. The follicle progressively increases in size, and the surrounding ovarian tissue, concomitant with the growth of the cystoma, undergoes pressure atrophy, until the atrophy reaches a stage where the blood-vessels are compressed and transudation ceases, and thus also the growth of the cystoma. The outer and inner surfaces of the cystoma are smooth and regular. The contents are a serous fluid; clear, yellow, mixed with blood, sometimes cloudy. Histologically, the walls are composed of a thin albuginea and dense connective tissue poor in cells and containing thin-walled blood-vessels. In most instances the inner surface of the cystoma-wall is free from epithelium; sometimes there is an epithelial lining, rarely cylindric cystomata. Those having epithelium Pfannenstiel believes are not follicular cysts, but true cystic new growths of the ovary. The follicular cystoma is of limited growth, a single cystoma rarely reaching a size larger than a walnut, or at most a baseball. A number of cystomata may cause the ovary to be the size of a man's fist. The confluence of cystomata may form a single cystoma.

It is probable that some follicular cystomata result from previous

inflammatory change in the ovary and surrounding tissue, as the ovary is not rarely found at the same time covered with inflammatory adhesions, or there is an associated inflammation of the tube or other ovary. Follicular apoplexies, no doubt, after the absorption of the hemorrhagic contents, sometimes become the follicular cystoma.

The follicular cystoma of the ovary is to be differentiated from other cystomata of the ovary by its smooth walls, limited growth, serous fluid contents, and by the fact that it neither macroscopically nor microscopically shows proliferative change.

Corpus luteum cystomata are retention cystomata of the ruptured Graafian follicle or corpus luteum. They are, as a rule, solitary cystoma of limited growth, not reaching a size greater than a walnut, but have been described as being the size of a fist and child's head. Two or more cystomata have been found in the same ovary. The wall is composed of an easily separable red, yellow, or ochre-yellow layer of tissue or membrane, made up of small capillaries embedded in pigmented round cells and leukocytes. The wall beyond this membrane is formed of the ovarian stroma-tissue. A hyaline membrane wall containing nuclei has been found in large cystomata. The contents are a thin, ropy, or syrupy fluid, red, brown,

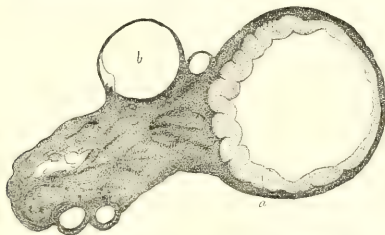


FIG. 348.—Cyst of the corpus luteum, showing the yellow lining membrane (a); b, small follicular cyst.

yellow, or resembling pus, and containing or composed of degenerated blood. The etiology of the corpus luteum cystomata is unknown, but, like the follicular cystoma, they probably arise from chronic hyperemia and inflammation.

Proliferating New Growth of the Ovary.—The morphologic classification of these tumors has been adopted for the following descriptions because it has seemed to the writer to be more scientific, accurate, and complete than the classification into cystic and solid tumors. Accordingly the proliferating new growths of the ovary are to be divided into three groups (Pfannenstiel)—those derived from the parenchymatous ovarian tissue (the parenchymatous new growths), those derived from the ovarian stroma-tissue (the stromatogenetic new growths), and the mixed new growths. The first group is further to be divided into those derived from epithelium (epithelial new-growths) and those derived from the ovule (the dermoid cystoma and teratoma).

The Parenchymatous New Growths (Epithelial New Growths).—**Simple serous cystomata** (cystoma serosum simplex (Pfannenstiel) appear as pedunculated, rarely as intraligamentous cystic tumors varying in size from an apple to a child's head. They have been described as reaching extraordinary dimensions.

Anatomically they are similar in character to the follicular cystomata, except that the internal surface is lined with a layer of normal proliferated epithelium, from which are secreted the fluid contents. They are benign, mostly unilocular cystoma. When multilocular, identical cystomata seem to have developed in juxtaposition, or possibly the multilocular character is formed through a proliferation and infolding of the epithelium, as in the cystadenomata to be described. The tumor in its growth, through pressure atrophy, more or less destroys the surrounding ovarian tissue. The walls are composed of dense connective tissue, covered on the outer surface with normal germinal epithelium and lined on the inner surface with a single layer of cylindric epithelial cells. The lining epithelial cells in the larger cystomata become distorted and flattened through pressure, sometimes undergo fatty degeneration or necrosis, and are partially or completely separated and mixed with the fluid contents. An epithelial lining resembling the syncytium is described.

Hemorrhages into the wall, as reddish-brown patches, may be seen; also patches of calcification. Papillary growths very rarely develop on the inner surface. They are short, warty outgrowths of limited and slow growth, composed of dense connective tissue covered with the epithelial lining of the cystoma-wall. The contents are a more or less clear, yellow or greenish, reddish brown when mixed with blood, serous fluid, having about the chemical and physical character of blood-serum. The sediment from the fluid contents contains a small amount of free fat, fat-cells, cell-detritus, and cholesterin-crystals. It is a tumor of slow growth. An arrest of growth with the absorption of the fluid contents is possible. With rupture the fluid contents are absorbed and the walls atrophy; more often the cystomacavity refills.

Little is known of the etiology of this cystoma. It appears to originate in the primordial and small follicles, possibly in the Graafian follicle. There is frequently an associated history of inflammatory processes, as puerperal fever and gonorrhea. Also it may be present with myoma of the uterus and other conditions producing chronic hyperemia of the ovaries.

Cystadenoma (glandular proliferating cystoma, cystadenoma pseudomucin (Pfannenstiel), the most frequent form of ovarian cystoma, is a benign, pedunculated, multilocular cystoma lined with cylindric epithelial cells (of the glandular type), from which cells is secreted a mucoid-like substance—pseudomucin. It is mostly a unilateral tumor (96 per cent.) of unlimited growth, sometimes reaching extraordinary size (116 pounds). The wall is composed of pure connective tissue containing blood-vessels, often formed into three layers in the largest or chief loculus—an outer layer of dense connective tissue, resembling the albuginea of the ovary, a central loose connective-tissue layer containing the larger blood-vessels, and a thicker inner layer containing the smaller blood-vessels. From the outer connective-tissue capsule surrounding the entire tumor, septa are given off to form loculi. The blood-vessel supply enters at the hilus, and is distributed through the walls to the entire growth. The loculi are of varying size and form. The tumor is usually composed of a larger or chief loculus, with numerous smaller loculi on and its walls. The chief loculus is formed partially by dilatation and partially through a confluence of loculi, the confluence resulting from thinning out, atrophy, and then rupture of septa. Bands of connective tissue or pockets in the wall of such a loculus

are usually present, indicating the position of a previous loculus. Such confluence of loculi can convert a multilocular into a unilocular cystoma. At other times the loculi are of equal size. In about 3 per cent. the tumor is composed simply of gland-ducts—pure adenomata. The external surface of the tumor is smooth and lobulated. The inner surface of each loculus is lined with a single layer of highly cylindric epithelial cells. In loculi of large size the cells are flattened out by pressure and often, in those of the largest size, show fatty or albuminoid degeneration, or necrosis or atrophy of the cells takes place and they entirely disappear. The inner layer of the connective-tissue wall frequently contains small, rarely large, calcification plates, indicating regressive metamorphosis. Also hemorrhages into the wall, atheromatous processes, fatty degeneration of the walls, and hemorrhagic infarcts occur. Papillary growths may rarely be found developing from the epithelium lining a loculus or from the germinal epithelium

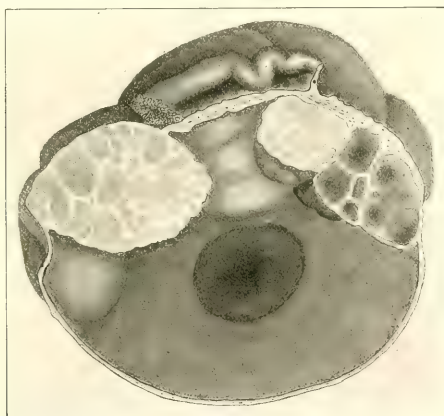


FIG. 349.—Cystadenoma of the ovary.

covering the cystoma. They are composed of connective-tissue elevations covered with cylindric epithelial cells. The contents of the loculi are excreted mostly from the cylindric epithelium lining, and, depending upon the degree of disturbance of the function or destruction of the epithelium, it differs in one loculus as compared with another. In the smallest and small loculi which, honeycomb-like, are formed together as a nodule in the tumor-wall, the contents are a pure, clear, tenacious, mucoid-like mass. In the somewhat larger loculi the consistency of the contents is that of honey; and in the largest loculus it is usually a thin, easily flowing, more serous fluid. Such mucoid-like substance is gray, yellow, or greenish in color from the presence of cholesterin; cloudy, opaque, or flocculent from the admixture of cells; and red or brown from the presence of blood. In the larger loculus the contents often lose the mucoid character, and consist of a serous fluid exudate from the capillaries of the cystoma-wall after destruction of the secreting epithelium. Microscopically the contents are a homogeneous

mass, containing fat-cells, cells resembling leukocytes, cell-detritus, and atrophied portions of septa. The fluid of the large loculi is rich in albumin, contains fat, cells, cell-detritus, and cholesterolin.

Chemically the substance excreted from the lining epithelium of the loculi is a peculiar mucoid-like substance—pseudomucin (Pfannenstiël). Three forms of pseudomucin are described by Pfannenstiël, and a substance called paramucin (Mitjukoff).

The etiology of this cystadenoma is not known. Theories of origin are—that they develop in duct-like infolding or ingrowths of new-formed germinal epithelium to the ovarian stroma-tissue, or in the persistent embryonal Valentine-Pflüger tubules. The closure and collection of secretions in such gland-like tubules explain the formation of the primary cystoma; and proliferation and further infolding of the epithelium, the formation of secondary loculi and the multilocular character. That multilocular character is to be explained by this process there seems to be no doubt. A third theory is that they originate in the Graafian follicle.

Through rupture of these cystadenomata, metastatic or implantation growths with cystic and pseudomucin formation can occur in the sub-peritoneal tissue (metastatic cystadenomata), or as implantations of pseudomucin masses on the peritoneum with chronic peritonitis (pseudomyxoma peritonei). Such growth can later become carcinomatous.

Serous cystadenoma, a rare form of ovarian cystoma, is a multilocular pedunculated, usually unilateral, tumor of slow growth, rarely reaching excessive size. The walls are composed of connective tissue, the outer surface being covered with more or less intact germinal epithelium, and the inner surface with fine cylindric epithelium having cilia. The cystoma-wall contains, particularly toward the pedicle, a large number of gland-tubules, demonstrating the proliferating character. A confluence of loculi takes place as in the preceding cystoma. The contents are a thin, clear, light-yellow or greenish fluid, alkaline in reaction and containing a large amount of albumin, but no pseudomucin. The fluid contents of large loculi may be cloudy from the presence of separated cells, or reddish brown from the admixture of blood. Briefly, this cystoma is characterized by its comparatively slow growth, the physical and chemical character of the contents of the loculi, and that the loculi are lined with fine cylindric ciliated epithelium.

Papillary cystadenoma.—Many authorities consider the papillary cystadenoma of the ovary to represent a separate group of proliferating glandular cystoma; others, as Pfannenstiël, state that the preceding cystomata not rarely contain papillary growths, and from the serous cystadenoma he believed the papillary cystadenomata develop.

The papillary cystadenoma is, as a rule, a bilateral, rather slow growing, either multilocular or unilocular (one-third) cystoma developing, in about equal frequency, either between the layers of the broad ligament as a sub-peritoneal tumor, or into the peritoneal cavity with a well-formed pedicle. When unilocular the walls usually show the indications of a previous multilocular character. When large and developing subperitoneally they displace and distort neighboring organs and separate the peritoneum from the pelvic walls and organs, even to the anterior abdominal wall. The walls are composed of connective tissue, as in the preceding cystadenomata, are richly supplied with blood-vessels, and contain microscopically

numerous small cysts. Papillary outgrowths of varying quantity and quality are seen growing from the internal surface of a loculus or loculi, often also upon the external surface of the tumor. They are diffusely distributed, circumscribed, most often to the wall opposite the pedicle, or a large loculus is completely filled with ramifying papillary outgrowths. The papillary growths are small (1–2 mm.) or large isolated or closely associated warty growths, or ramifying cauliflower-like masses the size of an apple or fist, having a broad base or are attached by a thin pedicle. They are red, granulated, often yellow from fatty degeneration, sometimes grayish-white from necrosis. The distal end of such papillæ may resemble in appearance swollen rice- or sago-kernels, formed like a bunch of grapes, from myxomatous change in the stroma-tissue. Frequently there is a calcareous deposit, sometimes concentrically deposited, resembling psammoma or sand-bodies. These deposits are found in the young as well as in developed growths, and are not a regressive change. The contents of the loculi are a clear serous fluid, sometimes cloudy from the admixture of cells, yellow or greenish. It is free from or contains only a trace of pseudo-mucin.

Histologically the papillary growths are composed of cylindric epithelial cells, mostly ciliated and proliferating, on a stroma of young loose connective tissue. The stroma-tissue contains few nuclei. It is abundantly supplied with blood- and lymph-vessels. The epithelium may be flattened, show fatty degenerative change, necrosis, become swollen or vesicular, and fuse together, so that a protoplasmic mass is seen infiltrated by many nuclei. The stroma may show fibrous change in old ramifying papillæ. Myxomatous degeneration of the stroma occurs as described. The papillary character is produced by an infolding or ingrowth of the proliferating epithelium into the connective-tissue wall, forming tubules, which tubules either develop into new loculi, or, more often, with progressive proliferation of the epithelium and hyperplasias of the stroma-tissue, they become papillary single or ramifying outgrowths.

The papillary cystadenoma is not malignant in the usual sense. The surface papillomata, or through the rupture of a loculus the papillomata contained in a loculus, are often separated and implanted on the pelvic peritoneum or the peritoneum throughout the abdominal cavity. Such implantation papillary growths, through excessive proliferation, may fill the abdominal cavity, cause ascites, and usually result in death. They are clinically carcinoma. Regressive changes have been known to occur after the surgical removal of the primary growth.

Superficial papillary adenomata (*surface papillomata*) are papillary outgrowths developing on the outer surface of the papillary cystadenoma, or on the surface of an ovary apparently not otherwise diseased. They are mostly secondary growths extending from a small ruptured loculus, or, less frequently, they develop from the germinal epithelium covering the ovary or cystoma. Such papillomata, through myxomatous degeneration of their distal ends, may resemble the hydatiform mole. Their macroscopic and microscopic character does not differ from papillomata above described.

Carcinomatous degeneration of the surface papillomata and papillary cystadenomata is not infrequent. According to Pfannenstiel, half of all papillary ovarian growths are of the type of adenocarcinoma. The stroma-tissue on which the papilloma develops is often infiltrated with epithelial cell-nests—papillary cystocarcinoma.

The histogenesis of the serous cystadenoma, and papillary cystadenoma likewise, is not definitely known, it being difficult to explain the origin of the ciliated cylindric epithelial cells. Also, since the papillary form frequently develops intraligamentous, an ovarian genesis is questionable. Theories of origin are: their development from the parovarian tubules of the paroöphoron (Waldeyer), from plaques of the tubal ciliated epithelium displaced in the ovarian stroma (Kassmann), or that the germinal epithelium under pathologic conditions is changed into ciliated epithelium, and through ingrowth or infolding causes the formation of these cystomata. The first theory has the greater number of believers.

Carcinoma of the ovary appears as a cystocarcinoma, less frequently as a solid tumor. The former is mostly a papillary cystocarcinoma or papillary adenocarcinoma. Carcinoma of the ovary is much less frequent than the cystadenomata (1-5, 5). It is found at any age, not rarely at puberty, but mostly between the ages of thirty and fifty years. It is usually a bilateral growth, but the development is not always synchronous. The solid carcinomata are either of the medullary or scirrhus type, forming ovoid-shaped or globular tumors. The medullary form rarely reaches a size greater than a fetal head. Its surface is white or yellow in color and slightly nodular. On section a diffuse medullary carcinomatous infiltration is demonstrable, sometimes showing areas of fatty or caseous degeneration or blood infiltration. Small cysts are occasionally found beneath the surface which have been formed through degenerative change, or they are cavities lined with epithelial cells. Scirrhus carcinoma is a tumor not larger than a fist, of the consistency of a fibroma, and has a smooth surface. It occurs at an advanced age. Histologically it is composed of epithelial cell-masses or -nests in a thickly interwoven, dense connective tissue. Rarely the medullary form is combined with a colloid carcinoma.

The cystocarcinomas have the form and shape of the cystadenomata. They are, however, smaller tumors, as a rule; not larger than a fetal head. The content of the loculi is a clear or cloudy serous fluid; or, through the admixture of cells, it resembles pus; or, from the presence of blood, blood. The walls and septa contain nodules and thickened areas of varying size, which on section show the changes of medullary carcinoma. The loculi are in places lined with a single layer of cylindric epithelial cells, in other places with many layers of proliferating polymorphous epithelial cells. They are mostly papillary carcinomata. The papillary growths do not differ in appearance from those of the papillary cystadenomata, but on section a milky fluid exudes and the microscopic character of carcinoma is demonstrable. The nodules show the character of a papillary adenocarcinoma, resembling the papillary carcinoma of the body of the uterus. Also small cystic cavities formed of connective tissue are seen, filled more or less with polymorphous epithelial cells. Papillary adenocarcinomata as papillary outgrowths are found on the surface of the tumor. Papillary adenocarcinoma developing from the surface alone is extremely rare. A portion of the tumor may show the character of a cystadenoma described, and another portion adenocarcinoma; the carcinomatous change appearing as a degeneration, or there is a synchronous development of the cystadenoma and adenocarcinoma. Gebhard describes the cystocarcinomata as always being a carcinomatous degeneration of a papillary cystadenoma or, more rarely, a degeneration of the cystadenoma.

Carcinoma of the ovary extends chiefly to the peritoneum; being first localized to the pelvic peritoneum, but finally producing an abdominal carcinomatosis. Metastatic ovarian carcinoma is rare. When present, it extends from carcinoma of the body of the uterus, stomach, mammary gland, or vaginal cervix uteri. The lapse of time between the development of the primary and such secondary growth is very great—as long as nine years. Therefore it is possible that such carcinomata are not metastatic, but associated in the individual predisposed to carcinoma.

Ovulogenous New Growths.—Dermoid cystoma of the ovary is believed to be a rudimentary embryo which has developed from the ovule within the ovarian follicle (Wilms). The origin of such a developmental change is thought to be an irritation of the ovule-cell similar to that of the epithelial cell in carcinoma (Pfannenstiel). The ovarian dermoid differs from that of other parts of the body in that it is derived from all three layers of the blastoderm, the tissue derivatives are formed in a position which at least resembles that of the embryo. The dermoid forms from 4 to 7.5 per cent. of all ovarian tumors, and has been found in the eight-month fetus and at every age thereafter, particularly during the period of sexual activity. They are rather thin-walled cystomata, from the size of a cherry-stone to that of a man's head, of slow growth (sometimes twenty years), and, like the cystadenomata containing pseudomucin, in their development more or less completely destroy the ovarian tissue, forming a pedunculated intraperitoneal tumor. Rarely they develop partially between the layers of the broad ligament, but never wholly so. A multilocular, or indication of a previous multilocular character, is sometimes seen. Frequently a simple serous cystoma or cystadenoma (mostly the cystadenoma containing pseudomucin, in one case the papillary cystadenoma) develops in an ovary with the dermoid cystoma, the dermoid cystoma being on the periphery or enveloped by the cystadenoma. According to Wilms, this association explains the presence of a multilocular character. The outer surface of the tumor is smooth and regular. The walls are formed of dense connective tissue. The contents of the cystoma is a thick, oily, sebaceous material, composed of yellow fat, shed hair, fat-granules, separated epithelium, cell detritus, and cholesterolin-crystals. On the inner surface of the wall at one point there is commonly a prominence, the so-called *parenchyma body*, which contains to a greater or less extent tissue derivatives, from the surface inward, of the ectoderm, mesoderm, and entoderm. The ectodermal tissues are best developed, being represented by a thin epidermis, made up, as a rule, of the stratum corneum, rete Malpighii, and an indistinct stratum cylindricum. The epidermis contains sebaceous and sweat-glands, hair-follicles, and hair, sometimes epithelial formations of the mouth, as a closed cavity or pocket on the surface, lined with squamous epithelial cells, which not rarely contains mucous glands. Teeth are found attached to connective tissue or bone on the surface or embedded in the parenchyma-body. Also brain-tissue with a central canal, a finger-like projection, and mammary glands have been described. The mesoderm derivatives represented are usually fat and connective tissue, and unstriated, rarely striated, muscle-fibers, bone, as rudimentary cranial bones, more rarely maxillæ, and extremely rarely ribs and the bones of the extremities. The ectodermal derivatives are least developed, being at most represented by canals covered with cylindric or ciliated epithelial cells, or indications

of the mucous membranes of the intestinal and respiratory tracts. The remaining portion of the cyst-wall may be lined with cuboidal, cylindric epithelial cells, or cells having the form of the pseudomucin epithelium.

Dermoid cystoma tends easily to become infected with pyogenic bacteria, and inflammation and suppuration take place. Rupture is followed by peritonitis, usually of a pyogenic character. Rarely there occurs through rupture a dermoid implantation metastasis to the peritoneum. Adenocarcinoma and squamous epithelioma of the dermoid cystoma may occur, the former being a carcinatous change in the complicating cystadenoma.

Teratoma is an atypical modification of the dermoid, bearing the relation to the latter similar to that of carcinoma to the cystadenoma. While in the dermoid the chief mass of the tumor has a cystic character and the cystic cavity contains the secretions from the epidermal tissue, the teratoma is chiefly a solid tumor, and the productive activity of the cells is a proliferation process.

Teratomata are extremely rare. Like the dermoids, they are found in the young as well as in the adult. They are well-pedunculated nodular tumors, with a smooth surface, are usually larger than an adult's head, reaching sometimes an enormous size. The capsule is composed of connective tissue, often containing the remains of an ovarian parenchyma. On section irregular masses of dermoid tissue of various size, form, color, and consistency are seen separated by connective-tissue fasciculæ. The tissue is infiltrated with small cystic cavities (dilated glands or degenerated areas) having either a smooth or undulated surface. The teratomata have been found to contain connective tissue, mucous tissue, cartilaginous, bone, and fat-tissue, gland formations of cylindric, ciliated, or mucous epithelium, epidermal growths with sebaceous glands, sweat-glands, and hair, brain-tissue, eye-tissue with pigmented cells, and intestinal tissue. The tumor is characterized by an atypical arrangement, form, and structure of the epithelium (after the type of a carcinoma), and an excessive growth of embryonal connective tissue (after the type of a sarcoma). It is extremely malignant, being destructive and distributed by metastasis and implantation.

Stromatogenetic New Growths.—Fibroma and **fibromyoma** are found usually as a diffuse hyperplasia of the entire ovarian stroma, forming a tumor, hard in consistency, with smooth or somewhat nodular surface, the size of a walnut to that of a man's head. They are mostly unilateral tumors, composed of interlacing fibrillary connective tissue, and often contain a small, rarely a large amount of unstriated muscle-fiber. Not infrequently cystic cavities are seen in the substance of the tumor, which are dilated gland-spaces or lymph-spaces or blood-vessels, degenerated areas, or rarely a fibroma is combined with a cystadenoma. A condition of lymph-angiectasis or telangiectasis can occur; also fatty myxomatous degeneration, necrosis, or calcareous infiltration. Fibromata form from 2 to 3 per cent. of ovarian tumors. They have been found at every age between eight and seventy-two years, mostly between forty and sixty years of age. Circumscribed fibromata, a partial hyperplasia of the ovarian stroma-tissue, appear as small nodules, not sharply outlined, embedded in the ovarian stroma or as nodular surface prominences. Small indifferent warty fibroma sometimes develop on the surface of the ovary—papillary fibroma.

Corpora fibrosa (*fibroma of the corpus luteum*) is a round, circumscribed

nodule, reaching the size of a walnut or that of a hen's egg, formed of a central fibrous mass and an outer laminated membrane.

Sarcoma appears as a pedunculated tumor similar in size to the fibroma. The surface is commonly smooth, the consistency variable, mostly softer than a fibroma. It is a spindle-cell or round-cell growth arising diffusely from the ovarian stroma-tissue. The spindle-cell sarcoma is of dense consistency, and on section shows a fibrillary character. It is to be differentiated from the fibromata, first, by the presence of a more heterogeneous division of cells—groups being seen in which the elements are very closely packed together, while in the neighboring field the relation or division of cells is similar to that of the fibroma. Such a differentiation is demonstrable macroscopically by the irregular coloring of tissue. Second, by the variously formed and large-sized cell-nuclei, which take the stain deeply. The round-cell sarcoma is softer in consistency. Histologically it is composed of large strata and nests of round cells, containing single giant cells and blood-vessels of various caliber. Fibrillary connective tissue is present only in a small amount. It is sometimes seen developing from the outer walls of small and middle-sized blood-vessels. Such tumors, according to Rosthorn, have their origin in the endothelium of the perivascular lymph-vessels—endothelioma perivascular. Others believe they develop from adventitious connective tissue in immediate relation with the blood-vessels, and are in the same tumor (Amann). Spindle- and round-cell sarcomata are frequently combined. A spindle-cell sarcoma can contain considerable fibrous tissue—fibrosarcoma. Myxomatous change can occur in both forms—myxosarcoma. Sarcoma may be combined with adenoma; as a sarcomatous degeneration of the wall of an ovarian cystoma. Hyaline degeneration, fatty degeneration, necrosis, hemorrhage, thrombosis, and, not rarely, lymphangiectasis occur. Sarcomata are often bilateral in growth, particularly the round-cell form. They are found at every age, as early as the seventh month of fetal life. Those of childhood are round-cell sarcoma. The round-cell sarcoma is very malignant, being destructive to surrounding tissues, gives metastasis to the peritoneum, and through the blood- and lymph-channels to distant organs. The spindle-cell sarcoma is less malignant, and the fibrosarcoma only slightly malignant or nonmalignant. Metastatic sarcoma, mostly from the uterus, is rare.

Endothelioma, not a very rare form of sarcoma of the ovary, has its origin in the endothelial cells of the blood—endothelioma vasculare—or lymph-vessels—endothelioma lymphaticum. The macroscopic character of the endothelioma is very variable. It appears as a unilateral, often as a bilateral, hard or soft, solid or partially cystic tumor having a smooth or nodular surface. Morphologically it may resemble the type of a carcinoma, sarcoma, adenoma, or the various mixed forms of new growth of the ovary. Histologically three types of cellular structure are described by Pick: First, the formation of roset or bead-like chains composed of masses of cuboidal to cylindric epithelial-like endothelial cells, running parallel with which are two or more layers of fibrous fasciculæ. Such bead-like cell-chains communicate one with another and are separated by connective-tissue stroma. On transverse section they appear as canals filled with a small amount of lymph or blood. Second, a type where there are gland-tubule-like formations, the tubules having a distinct lumen. In other areas the arrangement of cells strongly resembles that of an adenoma or adenocarci-

mona, but the cells are determined to be derived from endothelium. The endothelial growth is composed of polymorphous cells. The gland-tubules may be filled with lymph, dilated and fused together, forming tortuous worm-like cavities. Third, a type showing a diffuse sarcomatous structure with an indistinct alveolar relief. The alveoli are formed of masses of round epithelial-like bodies, parenchyma cells, which, through accurate focussing, are seen separated by a thin fibrillary intercellular tissue. All three types, with one predominating, are frequently found in the same tumor. The cells of the endothelioma, particularly in the lymphatic form, are generally smaller than those of carcinoma, and their origin in the endothelium of the lymph- and blood-vessels is usually to be determined. Hyaline and myxomatous degeneration of the stroma-tissue occurs. They are very malignant tumors. An endothelioma combined with a cystadenoma is described. Also a peculiar mucous softening of an endothelioma under the name fibrosarcoma ovarii. Under the name perithelioma, a form of sarcoma is described which has its origin in the adventitious connective tissue found immediately surrounding blood-vessels (Amann).

Angioma of the ovary very rarely appears as a unilateral or bilateral growth in an individual having a general disposition to angioma formation.

Complications of Ovarian Tumors.—Torsion of the Pedicle.—

More or less torsion or twisting (as many as six complete twists) of the pedicle of an ovarian tumor is not infrequent. There is usually compression of the blood-vessels contained in the pedicle, mostly the veins, with venous stasis and characteristic pathologic changes in the pedicle and tumor, the extent of such changes depending upon the rapidity and degree of torsion. The pedicle at the position of torsion is often thinned. Distal to this point the Fallopian tube and broad ligament are enormously swollen and dark bluish-red in color from the suffusion of blood. The tumor shows a similar change; it is enlarged through venous stasis, distended, tense, and of the same color. The tissues of the solid and walls of the cystic tumor are either edematous or infiltrated with blood. The fluid contents of the cystic tumor are blood red, often chocolate color. In older cases the fluid contents are of a yellowish color, the walls often an intense orange yellow, the lining epithelial cells are destroyed, and replaced by a granulation membrane. Hyaline degeneration and calcification of the connective-tissue wall are frequently present. The swelling and tension in a cystic tumor may easily cause rupture with hemorrhage, rarely fatal, into the peritoneal cavity. More frequently there results an acute peritonitis with fibrinous exudate and then fibrous adhesions. The peritonitis probably arises from the mechanic irritation of the tumor; possibly the change in the tumor forms chemical products which are irritating to the peritoneum. Necrosis of the tumor, partial or complete, may follow when the blood-supply is completely obstructed. Also infection and suppuration of the tumor may occur. The pedicle may be twisted off and the tumor lie free in the peritoneal cavity; or it becomes attached to other structures and nourished by the blood-vessels of adventitious tissue.

Inflammation and **suppuration** of an ovarian tumor may occur; their etiology being similar to that of acute oöphoritis. The dermoid cyst particularly has this tendency.

Rupture of the ovarian cystomata often takes place through thinning of the walls, torsion of the pedicle, traumatism, or spontaneously, the fluid

contents being discharged into the peritoneal cavity. If serous, the fluid is absorbed without irritation. The influence of the discharge of pseudo-mucinous or papillomatous masses into the peritoneal cavity has previously been referred to. The discharge of pus containing virulent micro-organisms is followed by a diffuse purulent peritonitis. The rupture of a unilocular retention cystoma results in atrophy and its complete or partial disappearance. The proliferating cystomata usually refill and continue to grow.

Parovarium Cystoma.—This cystoma is a cystic dilatation of the longitudinal or vertical tubules of the parovarium. It is a unilocular, sometimes multiple, small (often bilateral) to very large flaccid cystoma developing between the peritoneal layers of the mesosalpinx, the tube and ovary, ovarian and tubo-ovarian ligaments. The larger tumors have a

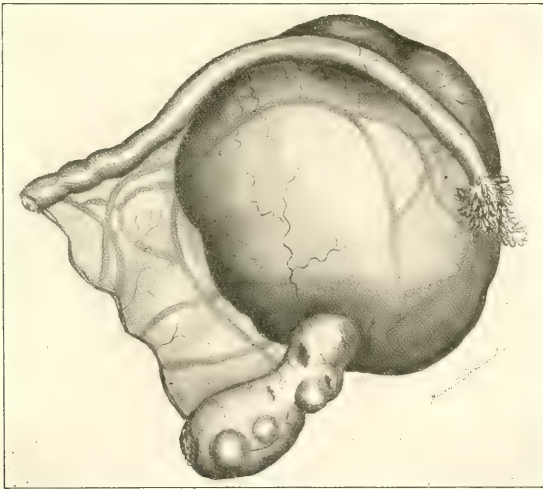


FIG. 350.—Cyst of the parovarium; there is no distortion of the ovary; the Fallopian tube has been much elongated.

pedicle formed of the tube and ovarian ligament, or the cystoma grows downward between the layer of the broad ligament—intraligamentous. The wall is composed of a thin layer of fibrillary connective tissue, covered with easily separable peritoneum containing the blood-vessels. The inner surface of the wall is lined with a single layer of ciliated cylindric epithelial cells. In large cystoma the cells have lost their cilia, are flattened and often destroyed. The contents are a clear, serous, alkaline fluid (sp. gr. 1005); in large cystoma sometimes cloudy, yellow, brown, or thickened from fatty degeneration of the wall or hemorrhage into the wall. Short, thick, watery connective-tissue growths are occasionally found on the inner surface of old cystomata (papillary fibromata). Also a large cauliflower growth developing from the inner wall has been described—parovarium papillary cystadenoma.

THE PELVIC CONNECTIVE TISSUE.

Circulatory Changes.—Varicosities of the veins of the pelvis, pampiniform plexus, are found caused by the compression of these veins by the pregnant uterus, uterine and ovarian tumors, or from venous stasis of chronic heart, lung, or liver disease. Also there may be phlebectases, phlebitis, phleboliths, arteriosclerosis, or an endarteritis of the pelvic vessels.

Hematoma in the pelvic connective tissue is caused by the rupture of varicose or diseased veins during labor, through external traumatism, or the rupture is spontaneous. They are localized or diffuse collections of blood, the size of a hen's egg to that of an adult's head. Their position may be between the pelvic diaphragm and the peritoneum of Douglas's cul-de-sac—retro-uterine hematoma; the ante-uterine portion of the pelvic diaphragm and visceral fascia—ante-uterine hematoma; at the base of the broad ligament—broad ligament or parametrial hematoma; in the upper portion of the vesicovaginal septum—retrovaginal or interstitial hematoma; and in the subcutaneous connective-tissue space—hematoma of the vulva or vagina. Also the rupture of a tubal pregnancy into the broad ligament may form a broad-ligament hematoma. The blood collection is usually absorbed; but infection, suppuration, and abscess formation may take place. Injuries, lacerations, and contusions of the vagina or uterus when extensive often involve the pelvic connective tissue.

Inflammation.—**Parametritis** (*pelvic cellulitis*), or inflammation of the pelvic connective tissue of the broad ligament, iliac fossæ, or that surrounding the vagina and cervix, is mostly a puerperal infection extending from the uterus, Fallopian tubes, or vagina, but may follow operations on the cervix, vagina, or broad ligaments, other acute inflammations of the genital mucous membranes, ulcerative processes of the rectum, and inflammation of the pelvic bones. The infecting micro-organism is usually a streptococcus, rarely a staphylococcus. The infection extends to the pelvic connective tissue through the lymph- and blood-vessels, or by contiguity. Gonococci, *Bacterium coli commune*, the diphtheria and influenza bacilli have been found. In the acute stage of the inflammation there are commonly a metrolymphangitis, perilymphangitis, and small round-cell infiltration of the connective tissue, with serous, often hemorrhagic, exudate and edema. In severe infections, puerperal, the inflammation becomes phlegmonous, progressing to suppuration and abscess formation. Also there occur an analogous venous thrombosis, metrophlebitis, edema, and abscess formation. The inflammation can be diffuse or localized. Metastasis to other organs is frequent. Abscesses may rupture into neighboring hollow viscera. Resorption of the exudate can take place with cicatricial change and adhesions; when extensive and diffuse, also with secondary atrophy of the genital organs. Collections of pus may remain for months or years in the pelvic connective tissue, the acute inflammation recur, and metastasis take place.

Gonorrheal parametritis is an exudative inflammation not tending to abscess formation.

Tuberculosis, as a tubercular infection extending from the uterus or peritoneum into the pelvic connective tissue of the broad ligaments, may occur, spread, cause caseation and abscess formation.

New Growths of the Pelvic Connective Tissue.—**Myomata** of the uterus extend into the pelvic connective tissue as intraligamentous or retrocervical tumors. Solid and cystic tumors of the ovary and the par-ovarian cystoma are frequently intraligamentous. Carcinoma of the uterus and vagina, when advanced, involves the pelvic connective tissue. Cystoma of Gärtner's duct may be found in relation with the lateral walls of the uterus. Fibroma of the round ligament may extend into the pelvic connective tissue. Pedunculated fibromyoma are described as arising from the connective tissue of the upper border of the broad ligament. Fibrosarcoma, fibromyosarcoma, telangiectatic sarcoma, cystosarcoma, medullary sarcoma, and chondrosarcoma have been found developing in the same position. Lipoma and myxolipoma of large size have twice been found arising, it was believed, in the connective tissue of the mesorectum and developing between the layers of the broad ligament. More frequently small lipoma have been found in the mesosalpinx and broad ligament.

Dermoid cystoma, varying in size from a pigeon's egg to a child's head, primarily develop in the retrorectal connective tissue, the connective tissue of the broad ligament, or between the peritoneum of Douglas's cul-de-sac and the levator ani muscle (24 cases, Sängner and Beyea). Such primary dermoid cystoma of the pelvic connective tissue are in no way connected with the ovary, but, it is believed, result from infolding of the blastoderm.

A **lymphatic cystoma** of the broad ligament has been described.

Accessory suprarenal bodies, the size of a large pinhead, have quite frequently been discovered in the outer half of the broad ligament in the fetus, newborn infant, and child up to the age of four years. They may form small cystoma or small hyperplasia.

Echinococci, primary or secondary, are rarely found in the pelvic connective tissue.

THE PELVIC PERITONEUM.

Perimetritis or **pelvic peritonitis** often occurs with or follows puerperal or other forms of inflammation of the uterus, tubes, ovaries or parametrium. It commonly extends directly from the inflamed part. Pelvic peritonitis also sometimes extends from the bladder, vermiform appendix, rectum, and pelvic bones. More or less peritoneal inflammation occurs with the pelvic hematocele. The inflammation is fibrous, sero-fibrinous or purofibrinous, mostly terminating in the formation of cord-like or membranous adhesions between the various pelvic organs. Such adhesions are found between the posterior wall of the uterus and anterior wall of the rectum, the ovaries and fimbriated extremity of the tube, the uterus and bladder, intestines and omentum. The inflammation may be purulent or putrid in character, particularly that of puerperal origin, forming adventitious abscesses or progressing to general peritonitis. In recent pelvic peritonitis, inflammatory exudate, becoming clear serous fluid, may be found between adhesive membranes, giving the appearance of cystoma formation. Hemorrhage from the richly vascularized adhesion membrane, peritoneum, tubes and ovaries may also collect as serous fluid or coagulated blood between the adhesive membranes.

THE BREAST.

THE FEMALE BREAST.

THE development of the female breast through its consecutive periods of advance, activity, and decline affords us the most satisfactory working basis for a classification of its manifold morbid conditions.

The mammary gland is an ingrowth of the epidermal layers of the skin, taking its origin, according to Minot, from the sudoriparous glands. At birth the gland consists only of a series of radiating ducts with ectasic club-shaped extremities. During the first year the proliferation of the epithelial lining of these ducts may become so active as to give rise to the swelling known as the *acute mastitis of infants*. No other material change takes place, however, until the age of puberty, when in the female the epithelial elements undergo rapid proliferation and form acinous gland-structures, communicating with the pre-existent ducts. This process is also present in



FIG. 351.—Normal adult female breast, showing periacinous connective tissue with many nuclei (low power).

the male breast, but to a much less degree. At this period also a hyaline connective tissue, rich in nuclei, makes its appearance, surrounding the gland-acini, and easily differentiated from the firm connective-tissue stroma of the gland (Fig. 351).¹

¹ The microphotographs in this chapter were taken in the Pathologic Laboratory of the Massachusetts General Hospital.

During pregnancy the acini increase rapidly in number, and the gland becomes more vascular ; while after lactation the number of acini is again diminished, and their place is taken by adipose tissue. The fibrous stroma of the gland, however, never regains the firm and elastic condition which it had before lactation.

After the menopause a marked retrograde process takes place in the breast, with atrophy of the gland-elements and increase of fibrous and adipose tissue. The deposit of fat obscures the atrophic changes to a certain extent, but the increased firmness and loss of elasticity are, as a rule, to be detected.

Infantile hypertrophy is a rare condition, and results from a slight exaggeration of the normal proliferation that occurs in the first year of life.

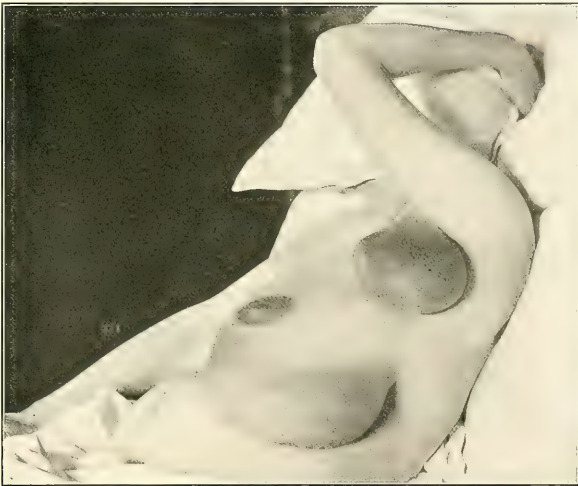


FIG. 352.—Polymastia and diffuse hypertrophy of the breast.

Such a growth may give rise to the precocious appearance of a well-formed breast-gland in a child two or three years of age.

Amazia and Micromazia.—Complete absence or incomplete development of the gland is a rare phenomenon, occurring, as a rule, in association with other malformations or developmental defects.

Polymastia.—Supernumerary breasts are not especially uncommon. As a rule, they occur on the so-called milk-line seen in the embryo of the lower animals, and for this reason may be regarded as an instance of atavism or reversion to a lower type. In the human being the extra glands are most often found below and inside of the normal situation or upon the border of the axilla ; but they do not always occur in pairs, and cases have been reported in which well-formed breast-structures have been found in remote situations, as upon the labium or the thigh.

Atrophy of the breast (*atrophy of the mammary gland*) occurs

normally after the menopause, but occasionally precedes that period, and may then be regarded as pathologic. Removal of the ovaries in early life has been followed by atrophy of the breast; but this is not generally the case. The development of adipose tissue in the stage of involution obscures the atrophy of the gland-elements.

Diffuse Hypertrophy of the Breast.—This is a rare affection, and differs only in degree from the physiologic increase of the component parts of the gland that normally takes place at the age of puberty or in early pregnancy. The condition occurs early in sexual life. There is probably a true new formation of gland-tissue (adenoma), and in many cases fibromas are found. The total size of the gland may be increased to so great an extent as to cause marked disability. In one case reported by Williams the breast weighed 64 pounds (Fig. 352).

Inflammations of the Breast.—**Acute mastitis** occurs almost invariably at the period of lactation, although rarely observed at the time of puberty and in the course of specific infectious diseases, as in mumps. The mastitis of infants and that occurring in infectious diseases rarely proceed to suppuration. During lactation the process begins generally in one of the lobules of the gland, with swelling and infiltration, and may go on to suppuration and abscess formation. Infection generally occurs from the nipple, and the staphylococcus and streptococcus are the bacteria most frequently found. The process may subside without suppuration, or an extensive abscess may be formed, involving large portions of the gland or dissecting it up from the chest-wall.

Chronic Diffuse Mastitis.—This is not infrequently the result of a previous acute process, and is characterized by a marked proliferation of the connective tissue and subsequent contraction, with induration and atrophy of the gland-structures. Such a condition is found, as a rule, in the later periods of life; and may occur independently of any known acute process; and accompanied by involution cysts, in which case it is to be regarded as merely an exaggeration of the physiologic retrograde changes belonging to the menopause. In some cases proliferative changes of the epithelium accompany the atrophic process, and a confused mass of cysts and ducts clad with several layers of partially degenerate epithelium may result—the condition often described as “chronic mastitis with retention cysts.”

Chronic mastitis may involve the whole gland or only separate lobules, and has been mistaken clinically for scirrhus cancer; although in some cases undoubtedly the reverse is true, that cancer has been mistaken for mastitis.

Tuberculosis of the breast is a comparatively rare affection, and has been described as occurring in two forms—disseminated and confluent. Infection is generally from a tuberculous focus in some other part of the body, either by external contamination or by retrograde infection through the lymph-channels, and it is doubtful if primary tuberculosis of the breast occurs at all. The lesions are similar to those of tuberculosis elsewhere: A diffuse tuberculous tissue or the formation of multiple tubercles. Cold abscess is the extreme type of the confluent form of the disease.

Syphilis of the breast occurs in all stages of the disease, and presents no peculiarities in this situation. Primary lesions, secondary mucous patches, and eruptions and gummas have been observed, and a diffuse syphilitic mastitis of the whole gland has been described.

Actinomycosis.—Intrathoracic actinomycosis may extend to the breast; in one or two instances a primary actinomycosis has developed after the use of poultices.

Tumors.—Fibroma.—The present nomenclature of the benign tumors of the breast is much involved, and for this reason stress has been laid upon the development of the gland, with a view to reducing the classification to a more rational basis. Mention has already been made of the hyaline connective tissue with many nuclei that surrounds the gland-acini, and makes its appearance at about the age of puberty (see Fig. 351). It is from this tissue, according to Billroth, that the fibromas and sarcomas arise. The ducts, however, which are closely associated with this hyaline connective tissue are also involved to a greater or less extent, and it is the involvement

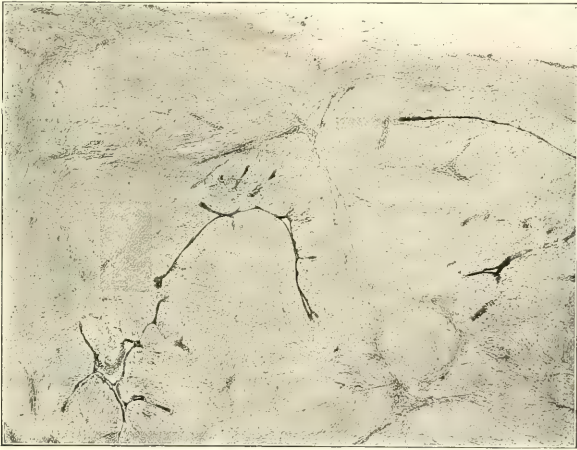


FIG. 353.—Fibroma of the breast (low power).

of the epithelial structures that determines the division between solid and cystic fibromas.

Solid Fibroma.—This tumor occurs usually in the breast of young girls—sixteen to eighteen years of age. It is a hard rounded mass, rarely larger than a walnut, well circumscribed and encapsulated, and generally situated at the periphery of the gland. On section the tumor is firm and fibrous in character, and with the microscope is found to be made up of more or less cellular fibrous tissue, with here and there a trace of the original gland-structures in the form of an elongated duct or bunch of atrophied alveoli (Fig. 353).

Cystic Fibroma.—The cystic form of fibroma belongs to a period slightly later than the solid form, and in this case the epithelial structures play a more conspicuous part, though still secondary to the connective tissue in which the tumors arise.

Cystic fibromas occur at about twenty years of age, and are found as nodular hard masses with well-defined outlines, situated in any portion of

the breast. On section the characteristic fibrous appearance is evident; but clefts and spaces are found scattered through the mass, representing the previously existing ducts and acini which have been dilated and distorted by the overgrowth of fibrous tissue. This distortion may present in many places the picture of coarse papillary projections, covered with flattened epithelium, occupying the clefts and spaces in the fibrous tissue; and thus the earlier names of intracanalicular papillary fibroma or adenofibroma. The type of this tumor, however, is the fibroma, and its origin is in the periacinous connective tissue, the epithelial proliferation being purely secondary (Fig. 354).

Adenoma.—Owing to the peculiar anatomic structure of the mammary gland, and its intimate association with all neoplasms of that organ, the term "adenoma" has been so freely used in the classification of tumors of the breast as to give rise to much confusion. During the functional activity of the gland the acini reach the highest point of development. They increase



FIG. 354.—Cystic fibroma of the breast (low power).

at this time enormously in numbers and grow out into the surrounding interstitial tissue. It is to those tumors that resemble most closely the breast-tissue at this period of physiologic activity that the term "adenoma" should be given. Adenomas should therefore include only those growths in which there is a distinct and independent new development of glandular parenchyma, and the term should rigidly be excluded from those new formations in which pre-existing mammary gland-tissue is found, even though that tissue may have undergone many incidental transformations. The tumors in which the purest type of new-formed acini are found are those known as villous papilloma. Many of the so-called "duct-cancers" are probably of this character. New acini are formed by a proliferation of cells from the pre-existing acini. The acini are dilated, the interstitial tissue breaks down, the cells assume a columnar shape, and the growth, at first typically glandular in character, becomes papillary. Secondary dilatation of the ducts occurs, and cysts form, which are at first filled with the

new growth, but later become much distended by a bloody fluid, which oozes from the surface of the highly vascular tissue. Hence the term cystic adenoma. The disease may be recognized by the cystic character of, and the presence of a bloody discharge from, the nipple. It occurs in middle life, and is a benign growth (Fig. 355).

In cases of diffuse hypertrophy of the breast there is also often a large increase in the amount of true glandular tissue. The fact that cancer is sometimes found in the walls of cysts of the mammary gland is regarded as proof by many that adenomas may become malignant; but it is not probable that they possess any greater tendency to malignant degeneration than other tumors of the breast.

Cysts.—During the process of involution of the breast, at the time of the menopause, a certain number of smaller ducts are cut off by the new-

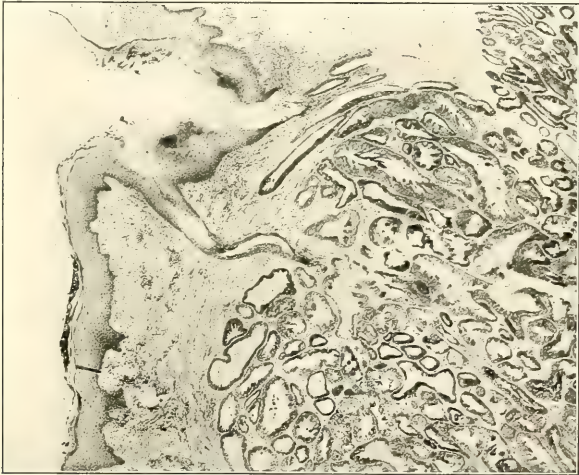


FIG. 355.—Adenoma of the breast in a large duct near the tip of the nipple (low power).

formed connective tissue, and persist as small shot-like nodules scattered through the glistening fibrous stroma of the gland, and containing fluid of a brown or greenish color, due to blood-pigment. These involution-cysts are so common as to be practically a normal appearance, but assume pathologic importance in certain cases in which, through the size of the cysts or their number, a tumor-mass is felt which sometimes is so hard as easily to be mistaken for carcinoma. In many cases both breasts are the seat of involution cysts. By their growth they gradually disorganize the remaining gland-structures.

Retention-cysts may occur during the active period of the life of the breast and present no especial peculiarities. When formed during lactation these cysts contain milk or its derivatives (galactoceles).

Lipoma, Chondroma, Osteoma, and Angioma.—These tumors occur

in the breast, but present no peculiarities in this situation. They are very rare.

Sarcoma.—Sarcoma of the breast is a comparatively rare disease, although one form, the cystic sarcoma, may be regarded as peculiar to this organ, and the most common of the sarcomatous tumors in this region.

Cystic Sarcoma.—The hyaline and cellular periacinous connective tissue that appears in the breast at the age of puberty has been shown to give origin to a tumor peculiar to it—the benign cystic fibroma. This same tissue also gives rise to a malignant tumor of like peculiarities—the cystic sarcoma. Such sarcomas are found as large embossed, succulent tumors, with a tendency to pedunculation and encapsulation, and occurring generally in early adult life. On section such a tumor is found to consist of numerous clefts or spaces, filled with mucus or hemorrhagic contents, into which project the papillary masses, clad with atrophic epithelium, which were characteristic of the cystic fibroma. In place of the delicate fibrous stroma, however, in the sarcoma a cellular tissue is found, made up of spindle- or round cells in greater or less number, with many blood-vessels. Areas of myxomatous tissue may be found, and cartilage and bone are rarely seen.

Solid Sarcoma.—Solid sarcoma of the breast, in contrast to the cystic form, arises in the fibrous tissue of the gland, and presents no characteristic appearance to distinguish it from sarcoma in other parts of the body. Such tumors may be made up of large or small cells, round, spindle-, or giant cells, and may present a solid or an alveolar arrangement. They are extremely rare.

Carcinoma.—The breast is one of the most frequent situations for carcinoma—40 per cent. of all cases of carcinoma being stated by Williams to be in this organ. Carcinoma is, moreover, by far the most frequent tumor in the breast. It occurs most commonly in the period of life immediately preceding the menopause, but has been found in rare cases at as early an age as twenty-one years (Gross).

The etiology of cancer is at present much in dispute, many theories and little proof being advanced upon this subject. Heredity, trauma, and parasitic causes have each their advocates; but the real cause of cancer is as little understood to-day as ever. Much systematic study of the disease, however, has been instituted in the past few years, and the outlook is more promising than heretofore.

Varieties.—The most rational and convenient method of classifying the different forms of carcinoma of the breast is that based upon the nature and amount of the cell-elements in the morbid tissue. By this plan a rough division may be made into medullary or scirrhous forms of growth, according as the epithelial elements are abundant or few in number in comparison with the connective-tissue stroma. This classification will not be found absolute, however, on account of the variation between different parts of the same growth and the nature of the surrounding tissues.

The variations in size and shape of the epithelial cells are striking, and the gradual change shown between older and younger portions of the same tumor is a marked characteristic.

The general arrangement of the epithelial columns may be made the basis of a further classification in so far as they correspond to the typical glandular arrangement with a central lumen and peripheral cells; and Halsted has called attention to this adenocarcinoma type as one with a tendency to

localization, and even pedunculation, and with less frequent formation of metastases. The view of Hansemann, which correlates the degree of malignancy of a given carcinoma with the degree of departure of its cells from the type of cell in which it originates, would seem to support this observation with regard to adenocarcinoma.

In the tissues immediately surrounding the carcinomatous growth a more or less abundant infiltration of small round cells will usually be found, quite analogous to the similar infiltration in chronic inflammatory processes, and presumably an indication of the resistance of the body to the carcinoma invasion.

Scirrhus Carcinoma.—In this form the epithelial cells are few in number and the columns widely separated, being condensed between dense masses of fibrous tissue. The cut surface of such a tumor presents a uniform dry, gray appearance, and resembles old scar-tissue. With the microscope,

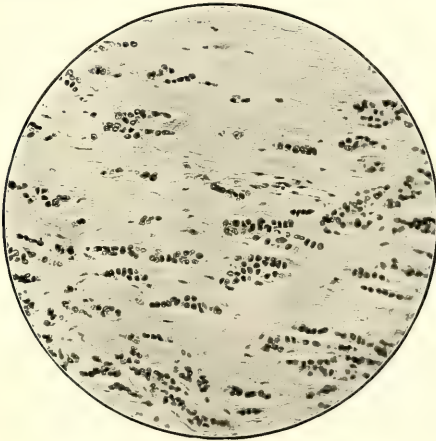


FIG. 356.—Scirrhus carcinoma of the breast (low power).

however, the characteristic epithelial elements are found, particularly in the periphery of the growth and in the metastatic deposits, although in extreme types of scirrhus degeneration may occur, and even calcification. The contraction of the dense fibrous tissue gives the name to this form of tumor and the characteristic shrivelled appearance to the breast (Fig. 356).

Medullary Carcinoma.—This class includes a variety of histologic pictures, but the gross appearance of such tumors is, as a rule, the same. A hard mass is found in the breast, with ill-defined outlines; on section the tumor is easily distinguished from the breast-tissue, and presents a reddish-gray surface, upon which are minute areas of white or yellow color of a softer consistency. Upon scraping the surface an abundant fluid may be obtained, which consists of the epithelial cells in the fat and serum of the tissue. The variation in cellular richness between different tumors is marked, and in some cases there may be very little stroma.

On microscopic examination the epithelial cells lie in broad columns, or in some cases in more slender columns, but so closely packed together as barely to afford room for the necessary blood-vessels and their accompanying connective tissue. In the center of the broader columns, at the point farthest from the blood-vessels, areas of fatty degeneration often occur, giving the picture of a central cavity filled with necrotic contents, and especially to be distinguished from the spaces occurring in less malignant cases of carcinoma, where an attempt at the formation of a gland-lumen may be detected in the orderly radial arrangement of the cells (Fig. 357). A division between acinous and lobular types of carcinoma, according to the arrangement of cells in columns either long or broad, was attempted by the

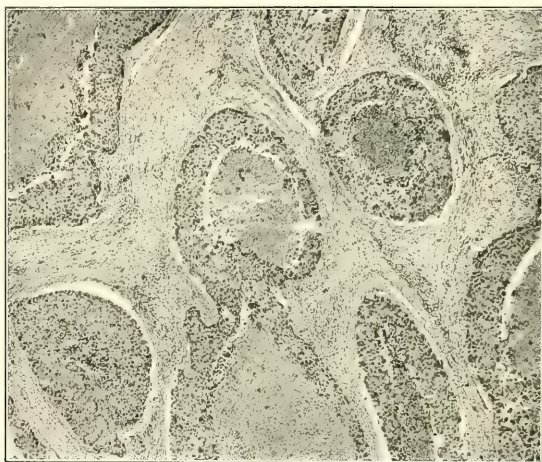


FIG. 357.—Medullary carcinoma of the breast, showing necrosis in the center of the columns (low power).

older pathologists; but this division is inconclusive, there being many cases which present both types.

Colloid Cancer.—This is an extremely rare form of cancer, and one which belongs to the less malignant forms. It derives its name from the transparent jelly-like substance which makes up the greater part of the tumor. Under the microscope the carcinomatous columns are found surrounded or infiltrated by a mucin-like substance, which in some cases is formed from the epithelial cells, in others from the connective-tissue stroma, but in all cases is thought to be a form of degeneration (Fig. 358).

Paget's Disease.—This disease is to be differentiated sharply from other forms of breast-carcinoma, and represents an entirely different process—epithelioma.

On the external skin of the nipple or areola an eczematous alteration takes place, with thickening and scaling of the epidermis and infiltration of the subcutaneous tissue. After a long period of comparative quiescence the infiltrating epidermal cells reach the ducts of the breast-gland, and there

produce an extensive invasion with epithelial cells of the squamous type. The origin of the cells, and the formation of epidermal structures like epithelial pearls, in the invading columns and the metastases, serve to differentiate the affection from the glandular form of cancer.

Carcinoma of the axillary border is a term applied by the writer to the form of carcinoma of this region in which the process begins as a lenticular nodule with elevated edges, in the skin over the pectoral margin of the axilla. From this point it extends into the breast itself, and its further course is similar to that of the usual breast-carcinoma. The tissue of origin is probably either a supernumerary mammary gland in this situation, or an unusual prolongation of that lobule of the gland nearest the axilla.

Metastasis.—In carcinoma of the breast metastasis may occur in the lymph-glands of the axilla, mediastinum, and neck, and in the skin, fascia,

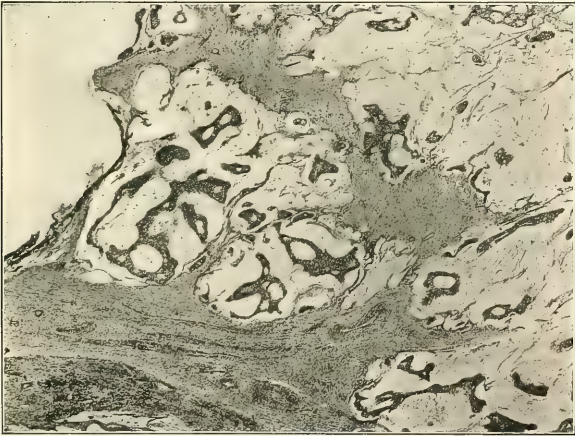


FIG. 358.—Colloid cancer of the breast (low power).

muscles, and bones of the chest-wall, or in the brain, viscera, and the bony skeleton.

Lymph-glands are the most commonly infected areas distant from the primary tumors, and their susceptibility to attack is thought to depend upon the fact that the spreading carcinoma seeks the spaces between the connective-tissue fibers of the part; and that these spaces are, in fact, the lymph-channels which ramify upon the surface of the body, and thus carry minute particles of the carcinomatous tissue to their respective systems of lymph-glands.

The axillary glands are most frequently involved, and after them the glands above the clavicle, about the subclavian vein, although in some cases, when the original tumor lies well to the inner side of the breast, direct involvement of the glands of the anterior mediastinum may occur. Infection begins in the periphery of the lymph-gland, and a repetition of the structure of the original tumor is found, care being taken to distinguish

from the endothelial proliferation in the lymph-sinuses, which occurs in many cases as the result of absorption of products of degeneration. Large masses may be formed by the matting together of infected glands or a spread of the growth to the surrounding areolar tissue (Fig. 359).

Skin infection occurs also through lymphatic channels, and may be far more extensive over the area of the tumor than is apparent to the naked eye. The epithelial cells lie in columns about the vessels immediately beneath the papillæ of the skin.

Invasion of the pectoral muscles is comparatively rare, except in advanced cases of the disease; but the fascia over them is frequently involved, and in some cases the lymph-vessels in these fasciæ appear as if they were injected with carcinoma-cells.



FIG. 359.—Lymph-gland with beginning infection from carcinoma of the breast, in vessels at the hilus, and in the sinuses at the periphery of the gland (low power).

The ribs and pleura are involved in advanced cases, but generally by contiguity rather than by metastasis.

Bone-metastases in carcinoma are one of the most marked features in some cases, whereas in others the bones seem to be immune. The whole medulla of the sternum, femur, or humerus may be invaded, and even the shaft eroded and replaced, by carcinomatous tissue; and fractures are not uncommon. Involvement of the bodies of the vertebræ and spinal compression and paralysis may also occur.

Visceral metastases occur most frequently in the liver, lungs, and brain. Large nodules may be found, which on examination show little but confused masses of epithelial cells invading and displacing the primary tissues of the part.

The cachectic condition of persons far advanced in general carcinomatosis

is extreme, and is due to the absorption of broken-down tissues formed in the progress of the disease.

THE MALE BREAST.

The male breast does not differ anatomically from the female breast until the age of puberty, and up to this time its diseases are also the same. At puberty an enlargement may rarely be detected in the male, with a mild type of inflammation.

Gynecomastia is the development in a man of a breast similar to that in the adult woman. Rare cases are reported in which even lactation has occurred. Such cases are not, as a rule, accompanied by anomalous sexual development, but do occasionally occur in connection with hermaphroditism. They are extremely rare.

Benign tumors of the same character as those in the female occur in the male breast, but much more rarely. Adenoma, cystic and solid fibroma, myoma, angioma, lipoma, and chondroma have all been reported.

Involution cysts have been observed in males, generally in the later period of life.

Tuberculosis is rarely met with in the male, but a form of chronic mastitis with induration and connective-tissue formation in men of forty-five to fifty-five years has been observed by the writer.

Scirrhus cancer is the malignant growth most frequently met with in the male breast, although medullary carcinoma and sarcoma have been observed. The majority of reported cases show a slow growth of carcinoma and late metastatic involvement, but the disease is otherwise similar to that met with in the female.

THE SKIN.

RETROGRESSIVE CHANGES.

Atrophy of the cutis and epidermis, or of portions of them, is a feature of many cutaneous diseases, and as such is described with them. It may also occur as the sole, primary, or chief change in the skin. A classification of the different cutaneous atrophies is impracticable without a better knowledge of their etiology and pathology than now exists. Two types are, however, generally recognized: the **quantitative**, in which there is a simple diminution in size or in numbers of the elements composing the skin; and the **qualitative** or **degenerative**, in which recognized degeneration of tissue occurs. Both types may occur together. In **senile atrophy**, the familiar condition seen in the skins of old people, there are, according to Neumann, general atrophy and usually increased pigmentation of the epidermis; flattening of the papillary layer and thinning of the corium; destruction of some vessels and enlargement of others; shortening of the hair-follicles and dilatation of the sebaceous glands; a disappearance of the fat-cells, leaving the connective-tissue meshes empty; and scattered cellular areas, which he thought relics of old inflammation, but which Unna regards as manifestations of senile involution. Neumann has also described a **degenerative senile atrophy** with coarse and fine granular degeneration and a vitreous swelling of the connective-tissue fibers. Schmidt, Reizenstein, and Unna find these microscopic appearances due to special groupings and arrangements of the elastic fibers, some of which undergo peculiar changes (manifested chiefly by their staining properties) into "elacin," or, in combination with the collagen, into "collastin" and "collacin" (Unna).

Atrophoderma striatum et maculatum (*striæ et maculæ atrophicæ*) occurs without known cause, though probably in many cases there is an unrecognized traumatic origin. These atrophic spots and striæ are often apparently neurotic manifestations, and in some instances are preceded by erythematous or hypertrophic lesions. Histologic examination in a few cases has shown simple atrophy of the tissues without degenerative changes. Rare cases of **idiopathic diffuse symmetric atrophy** of the skin have been reported by a number of observers, and have recently been carefully reviewed by Bronson¹ in reporting a case of his own. Elliott² and Fordyce³ have since reported each a case in which the progressive atrophy was preceded by a zone of capillary dilatation or cyanosis.

Secondary atrophy is seen as a result of the degenerative changes found in syphilis, tuberculosis, chronic inflammation, etc. It also occurs from traumatism, from pressure, as of slow-growing tumors, or from stretching, as in pregnancy, ascites, etc. In pressure atrophies, Unna describes an absence of elastic tissue, which is displaced or torn, and accumulates about

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, Jan., 1895.

² *Ibid.*, 152, 1895.

³ *Ibid.*, 230, 1897.

the borders. In atrophies from tension, he states that the changes are the same, except that in the striæ are still visible some small fibers of elastin, and fibers that have undergone regressive metamorphosis into "elacin," such as is seen in senile degeneration. These and other changes of the elastic fibers in the atrophies and in many other diseases of the skin have acquired a new interest with the recently discovered methods of technic, but the part they play in the pathology of the skin is not yet understood.

In the **multiple benign tumor-like new growths** of the skin described by Schweninger¹ and others, the primary change is probably an atrophy of the elastic fibers corresponding to that produced by tension, though the growths themselves show a hyperplasia of the sebaceous glands with cell accumulation. Among the rare, probably trophoneurotic, atrophies involving the skin and deeper structures may be mentioned the **glossy skin**, of Paget, Weir Mitchell, and others, which results from nerve injuries due to traumatism or disease; **perforating ulcer of the foot**, of which the exciting cause may be pressure or other slight local injury; **Morvan's disease** (*syringomyelia*), in which the analgesia, thermo-anesthesia, and mottling of the skin suggest local trophic and vasomotor changes; **kraurosis vulvæ**, an atrophy from unknown causes of the external genitals in women; and **ainhum**, the pathology of which is wholly unsettled, though there are evidences of chronic inflammation and the constricting ring, which eventually produces spontaneous amputation of the toe, is shown histologically to be made up of hyperplastic epithelium dipping down deeply between the other tissues.

Colloid metamorphosis of the skin (*colloid milium*) is a rare disorder in which the connective-tissue fibers and cells of the derma undergo colloid degeneration. The changes may be limited in extent or may involve considerable areas, and are most marked about the vessels, nerves, and sebaceous glands. The glands and epithelium, except the endothelium of the vessels, are not involved.

Symmetric gangrene of the extremities (*Raynaud's disease*) occurs in connection with different systemic disorders. It is thought to be neurotic in origin, the primary anemia being due to a spastic contraction of the capillaries and small arteries. The anemia may occur a number of times, the part being normal in the intervals, before it is followed by local asphyxia and edema with, possibly, extravasation of blood. Successive attacks of anemia and asphyxia are followed by impaired nutrition of the part, and finally by gangrene, which may develop suddenly or slowly, and is usually of the dry type, but may be moist.

VASCULAR DISTURBANCES.

The amount of blood in the skin varies greatly within physiologic limits, largely owing to the fact that the vessels have well-developed walls and are surrounded by tissue rich in elastic fibers. Thus the skin is well adapted to play the part of regulator of the circulation in functional disturbances of other, deeper-seated organs, and is frequently the seat of symptomatic anemias and hyperemias.

Anemia.—The skin may be anemic in common with the other organs

¹ *Internat. Atlas Selt. Hautkrank.*, Heft. 5.

of the body. Functional anemia of the skin alone is frequently encountered as a result of mental and emotional disturbances, as in fainting, nausea, etc., of nerve injuries, or of the excessive activity of other organs. Localized anemia of the skin may be caused by pressure from without or by spasm of the vessels. In the extremities, where the number of the vessels is small, such contraction may continue for considerable periods of time and produce the more or less permanent anemia found in the early stages of *Raynaud's disease*. Local anemia may also result from occlusion of the vessels by pressure from new growths or by endarteritis.

Hyperemia.—**Passive or venous congestion** of the skin is unusual unless due to mechanic obstruction, such as bandage, tumor, or new growth; or unless it be symptomatic of general circulatory disturbance. In *pernio* the anemia produced by cold is followed on removal of the cause by an active hyperemia, which in severe and persistent cases results in a passive congestion of the part. In passive congestion, dilatation of the vessels extends to the lower layers of the corium and even deeper, and is often demonstrable after death.

Active or arterial congestion of the skin occurs both as a physiologic and as a pathologic process. It is commonly symptomatic of functional disturbance or of disease of other organs, and is usually of short duration—lasting several hours or days. The anatomic changes are thus transitory, and cannot be recognized postmortem. The dilatation of vessels is usually limited to the papillary and upper layers of the corium, either in small circumscribed or in diffuse areas. In many of the so-called erythemas, however, the process does not stop with mere congestion, but goes on to true inflammation, with exudation, infiltration, and cell proliferation in varying degrees.

The *simple erythemas* may be due to mechanic or chemical irritation (*erythema traumaticum*); to heat (*erythema calorica*, *erythema ab igne*); to cold (*erythema pernio*); or to a combination of friction, moisture, and warmth (*erythema intertrigo*). If the cause is sufficiently severe or prolonged, any of the above forms of erythema may be converted into a dermatitis. Pigmentation may follow persistent or repeated attacks of erythema, particularly in *erythema ab igne* due to artificial heat.

In the *symptomatic erythemas* there is an obscure vasomotor disturbance, producing a dilatation of the capillaries and smaller arteries. It is evidently at times the result of reflex action, but in most instances is due probably to the presence of some toxin or irritant in the circulation, acting either on the nerve-centers or locally upon the vessels and nerves of the skin. The causes of these erythemas are many and diverse. They are found after mental or physical shock, after surgical operations; in many infectious diseases, such as typhus, dysentery, diphtheria, pneumonia, etc.; in rheumatism, gonorrhea, uremia, indigestion, and sewer-gas poisoning; and in some individuals after the ingestion of certain drugs or articles of food. In a large proportion of cases the idiosyncrasies of the individual form an important factor in the production of the erythema. This factor is probably of special importance in the type known as *erythema scarlatiniforme*, which runs a more or less definite course, is accompanied by fever and other constitutional disturbances, shows a marked tendency to recur, and would seem entitled to recognition as a specific disease but that it results from the most diverse causes. It usually terminates in slight desquamation, and gives

other evidences of the inflammatory nature of the process. The severer and more protracted forms, known as *erythema scarlatiniforme desquamativa*, are probably identical pathologically with *dermatitis exfoliativa*.

Purpura, or hemorrhage of the skin, is usually a symptom of systemic disease, although *idiopathic* cases, in which no cause can be discovered, are still described, and *traumatic hemorrhages* due to bruises, insect-bites, etc., must be recognized. Purpura frequently occurs in connection with arthritic and gastro-intestinal disturbances, the complexus of symptoms being known as *purpura rheumatica*. It is seen also in infectious diseases; after the ingestion of certain drugs or articles of food; as a result of blood alterations and of sudden changes in the circulation; in many nervous disorders, including diseases of the brain and spinal cord, neuralgias, dermatoneuroses, reflex disturbances, mental shock, and even autosuggestion in neuropathic individuals (Leloir). Blood escapes into the tissues through a ruptured vessel or by diapedesis, or there may be mere transudation of coloring matter. The process is usually situated in the papillæ and upper layers of the corium, whence the blood may pass up between the cells of the epidermis and to the deeper tissues, or it may occur rarely in the subcutaneous tissues and about or into the hair-follicles and sweat-glands. Various changes in the blood (Bensaude¹) and in the local vessels, as well as the presence of different bacteria (Finkelstein²), have been described. The origin of some cases may be found in toxemia or in direct infection.

HYPERPLASIAS.

More or less hyperplasia of different elements of the skin and subcutaneous tissues is found in many cutaneous diseases, and the formation of a class in which this is the conspicuous element is largely a matter of opinion and convenience. Regarding the hyperplasias of the epidermal layers, there exists at present an almost inextricable confusion in nomenclature, due to widely diverging views as to the nature of these processes.

Keratosis pilaris (*lichen pilaris*) is a term applied to small papule-like elevations about the hair-follicles. The adjectives *alba* and *rubra* are often added to distinguish noninflammatory from inflammatory types. The condition may be a mere accretion of physiologic secretion, with or without erection of the follicles by persistent contraction of the erectores pilorum. There is usually hyperkeratosis in and about the follicles, the mouths of which are filled with horny plugs. These first two types are usually limited to extensor surfaces. In the types in which inflammation is an added feature the condition may be found on the flexor and other surfaces (*lichen pilaris* of Crocker, *lichen spinulosus* of Devergie). Unna describes these conditions under the terms *keratosis suprafollicularis* (*alba et rubra*) and *keratosis follicularis spinulosa*. Brocq simply makes four grades of keratosis pilaris, the last and severest form including Unna's *ulerythema ophryogenes*, in which there is follicular and interfollicular atrophy with resulting cicatrices.

Keratosis follicularis (*Darier's disease*) is the name given by White to a rare disease of the skin first described by Darier³ as *psorospermiosis follicularis*. Most of the cases reported began in childhood. The etiology of the disease is not known, but heredity and contagion are suspected in some

¹ *Sem. méd.*, Jan. 20, 1897.

² *Berlin. klin. Woch.*, 496, 1895.

³ *Internat. Atlas Selt. Hautkrank.*, Heft 8.

cases. The histologic investigations of Bowen,¹ and the later ones of Darier² and other observers, show a primary hyperkeratosis and a parakeratosis involving the sebaceous follicles and hair-follicles. Darier and others state that the lesions may occasionally originate in the epidermis or about the mouths of the sweat-ducts. The mouths of the follicles are dilated and packed with funnel-shaped masses of imperfectly cornified cells. The process involves chiefly the neck of the follicle, but in the later stages extends to the interfollicular tissue. The characteristic changes are found in the rete, and consist of round bodies which strongly resemble psorosperms, but which are now generally conceded to be peculiar forms of cell degeneration; certain compressed, homogeneous, shrunken bodies, best seen at the bottom of the follicle-plugs, which Darier called "grains;" and fissures or lacunæ between the rete-cells, which result probably from the irritating pressure of the horny, round bodies, some of which are seen in the lacunæ. The rete usually undergoes marked proliferation and thickening, and in places grows deeply into the corium, producing papillomatous areas. The stratum granulosum is absent in the lesions. There are slight cellular infiltration in the corium and a deposit of pigment at the borders of the lesion in both corium and epidermis.

A **keratosis follicularis contagiosa** is described by Brooke³ and others, in which the appearances, clinically and histologically (in so far as they have been studied), are those of the various forms of keratosis pilaris. A rare form of keratosis affecting chiefly the sweat-pores has been described as *porokeratosis* by Mibelli, Respighi, Gilchrist,⁴ and others. Other unusual (or rarely recognized) forms are described by Unna and other authors.

Palmar and plantar keratoderma (*tylosis*, *keratoma*, or *keratosis palmæ et plantæ*) is a symmetric thickening of the horny layers of the palms and soles. The condition is uncommon, and is usually congenital or acquired in childhood, though it may follow hyperidrosis or the long-continued use of arsenic. Besnier describes four clinical varieties of the disorder, not including the temporary and usually patchy thickenings of the epidermis found in eczema, lichen planus, syphilis, and other affections of these regions. The process is a hyperkeratosis induced probably through the nerve-centers. The hyperemia present in Besnier's second type (*keratoderma erythematosa symmetrica*) is apparently secondary. The subacute affection described by Brooke as *erythema keratodes* is considered an inflammation of this region accompanied by hyperkeratosis.

Callus or callosity is a circumscribed thickening of the horny layers, due to traumatism in the form of intermittent pressure from without. The outer layers of the horny cells are pressed and welded together into a homogeneous dense mass. As this mass interferes with normal scaling, the middle portions of the horny layer are thickened, as is the granular layer. The rete, on the contrary, is usually thinned, and the papillæ may be more or less flattened by the pressure. Under continued or added irritation there may be active proliferation of the rete-cells, which then penetrate deeply into the corium, where they become cornified and welded together so as to produce a deep-seated callosity, which forms a center or core of a *clavus* or

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, June, 1896.

² *Ann. de Derm. et de Syph.*, 742, 1896.

³ *Internat. Atlas Selt. Hautkrank.*, Heft 7.

⁴ *Jour. Cutan. and Gen.-Urin. Dis.*, 149, 1899 (with bibliography to date).

corn. The base and surroundings of a corn are hyperemic, and the papillæ beneath are atrophied.

Cutaneous horns (*cornua cutanea*) begin, according to Unna, by simultaneously developed hyperkeratosis and acanthosis. The rete-cells grow down deep between the papillæ, which are thus thinned and lengthened, although some may be flattened out and obliterated. The granular layer is also thickened at first. After the papillæ are reduced to thread-like processes the acanthosis diminishes, while the keratosis increases until horny wedges are formed between the papillæ, from which they are separated by a few rete-cells, with possibly a single layer of granular cells. The cells immediately over the papillæ undergo a peculiar species of degeneration, forming hollow cells, coarse flakes, and granules. Thus each horn has as many medullary portions as it has papillæ at its base.

A **verruca** (*wart*) probably begins with hypertrophy of both the mucous and horny layers, the latter showing imperfect cornification (parakeratosis). The stratum granulosum is also much thickened. As the rete grows downward into the corium some of the papillæ are obliterated, but the vascular ones in the center of the wart enlarge and show dilated vessels. The descending rete-processes are usually pointed and turned toward a common center, producing thus a shallow, cup-shaped depression in the cutis. In the pointed forms (*condyloma acuminatum*) found about the mucous outlets of the body, the rete and papillary hypertrophy are most marked, the horny layer being comparatively thin. Various cocci and bacilli have been seen in the thickened epithelial layers, but their etiologic significance has not been demonstrated, nor are the causes of warts known.

Moles (*nevi*) may occur as overgrowths of the rete or of the horny layer, or of both, with the addition usually of an increased pigmentation. Frequently there is coincident increase in the number and size of the hairs of the area involved. Soft moles are described at length by Unna as "embryonic depositions of epithelia in the upper part of the cutis, which, by loss of their epithelial fibrillation, have lost their stiffness."

Acanthosis nigricans is a rare condition described by Pollitzer,¹ Darier,² Morris,³ and others, in which deeply pigmented, warty, and papilomatous growths appear over portions of the body. It has been associated a number of times with carcinoma of other organs, but Darier thinks it due to some lesion of the sympathetic nerve. Histologically the lesions show overgrowth of papillæ and of epidermal layers, marked dilatation of blood-vessels and lymph-spaces, increase of pigment in the palisade-cells, and down-growth of rete-pegs, with "suggestions" of epithelial pearls.

Ichthyosis is subdivided into a number of clinical varieties or degrees of severity, varying from *xerosis*, or *xeroderma*, which on the one side differs little from simple keratosis pilaris, and on the other shades gradually into *ichthyosis simplex* (*ichthyosis nacrée*, *ichthyosis nitida*), from which in turn may develop the severer grades (*ichthyosis serpentina*, *ichthyosis sauroderma*, *crocodile-skin*, etc.). *Ichthyosis congenita* and *ichthyosis hystrix* are distinct types. The disease usually begins in mild form during the first two years of life, and is probably due to an inherited predisposition or malformation, but its etiology and pathology are still open questions. In the mild forms Unna describes a marked hyperkeratosis which he considers characteristic

¹ Internat. Atlas Selt. Hautkrank., Heft 4. ² Ann. de Derm. et de Syph., Feb., 1895.

³ Med.-Chir. Trans., lxxvii.

of the disease in that the horny cells are formed directly from the rete without the interposition of the granular layer but nevertheless are homogeneous and contain no relics of nuclei as is usual in dry forms of parakeratosis. He cites these cases to uphold his belief, contrary to that of many observers, that keratohyalin is not essential to the process of cornification. The rete-cells are also characteristic in being small and poorly developed, and are separated by narrow spaces, thus making the process a peculiarly dry one. Over the papillæ there is frequently but a single layer of rete-cells. The papillæ are flattened but broadened, especially at their apices, and join in a sort of dovetailing process with the rete-pegs, which are broad below and narrow above. Excess of pigment is found chiefly in the palisade-cells. The epithelium of the coils of the sweat-glands resembles that of the duct, indicating diminished activity. In the cutis, Unna describes a thickening of the collagenous fibers which causes the disappearance of lymph-spaces, of the elastic net, and of the fat of the panniculus, and states that there are occasional inflammatory cell accumulations. In the severe forms he finds the rete combating the hyperkeratosis with active proliferation and hyperplasia, with the reappearance of the granular layer, producing thus a moister process, which may readily be transformed into the clinical crusting type known as "*ichthyotic eczema*." There is less superficial scaling than in the mild form, but the outer horny layers are denser and thicker, and the hyperkeratosis extends deeper into the rete-pegs. In the cutis the papules are larger, and many plasma-cells and mast-cells are seen.

Ichthyosis hystrix has, according to Kaposi, the anatomic structure of old warts, but Crocker states that the lesions differ from warts in that the horny formation dips down deeply, following the outline of the papillæ. **Ichthyosis congenita** (*harlequin fetus*) is an exceedingly rare and fatal deformity, the pathology of which is not known. Bowen¹ thinks it due to a persistence of the epitrighial layer of the fetus. Unna separates it from ichthyosis under the name *hyperkeratosis universalis congenita*.

Sclerema neonatorum is a rare, usually fatal, disease of the newborn, in which the skin rapidly assumes the clinical aspects of scleroderma. The affection may be congenital or may follow devitalizing conditions, such as diarrhea. In 3 cases Schmidt² found round bacteria in the capillaries and connective tissue. Langer thinks the cause of the sclerema lies in the solidification of fat. Parrot and Ballantyne describe a drying up of the skin, producing thickening of the horny layer, but thinning of the rete and cutis, diminution of fat, and possibly some increase of connective tissue, but no true sclerosis or serous infiltration.

Œdema neonatorum is a rare condition usually confused clinically with sclerema neonatorum, from which it is pathologically distinct. It occurs in infants born prematurely, in those exposed to cold soon after birth, and in others having feeble vitality from any cause. Histologic examination has shown an effusion of serum into the tissues, a remarkable density and yellowish-brown color of the fat, and in cases congestion of lungs and spleen, enlarged liver, nephritis, or thrombus of the femoral veins.

Scleroderma may be diffuse or circumscribed. Many circumscribed cases have special clinical features that entitle them to a distinctive name—*morphea*. Other clinical subdivisions are made, but so far as is known all

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, Dec., 1895.

² *Zeit. f. Geburt. u. Gynäk.*, Bd. xxii., Heft 2.

have a common pathology. The disease is more common in females than in males, and is most frequent in neurotic individuals or in connection with disease of the nervous system. Evidence in favor of its being a neurosis dependent upon changes in the nerve-centers is more frequently obtainable in morphea than in diffuse scleroderma. The diffuse form occasionally, morphea less frequently, appears rapidly after previous attacks of erysipelas, acute rheumatism, or exposure to cold. In 5 cases Singer and Beer¹ found decrease in size of the thyroid body. *Sclerodactylia* may be preceded by Raynaud's phenomena. In the majority of all cases of scleroderma no definite cause can be determined. According to Crocker and other observers the histologic changes are found in the corium and subjacent tissues, there being no changes in the epidermis except in those cases in which there

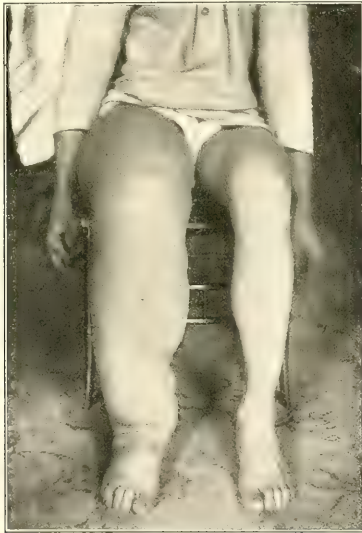


FIG. 360.—Elephantiasis (Riesman's case).

is an increase of pigment in the basal layer of the rete. Many of the vessels of the superficial plexus are narrowed, presumably by the pressure of groups of cells which form sheaths about the vessels, though in Schwimmer's case the narrowing was due to concentric hypertrophy of the intima and media. In a case of morphea Crocker found thrombi in some of the vessels. Masses of cells are seen about the sweat-ducts, hair-follicles, sebaceous glands, and in the panniculus adiposus. The cause and source of this cell accumulation are not known. There are no other signs of inflammation. In the papillæ the vessels are thinned and few in number. In older lesions there is hypertrophy of elastic and connective tissues and of muscle-fibers in the corium, with narrowing of lymph-spaces and lymph-vessels.

¹ *Berlin. klin. Woch.*, 446, 1895.

The connective-tissue growth may become deep and dense, and closely unite the upper layers of the corium with fascia or periosteum, and may produce atrophy of the hair-follicles, sebaceous glands, subcutaneous fat, coil-ducts, and exceptionally of the coil-glands.

Elephantiasis, in its typical and severe forms, is a common endemic disease of hot countries, where it is probably due to obstruction of the lymphatics by the *Filaria sanguinis hominis nocturna*, as has been all but proved by the researches of Manson (whose description¹ is largely followed here) and others. Manson has shown also that the female of a certain species of mosquito acts as intermediate host in transferring the filaria (which undergo metamorphosis in the tissues of the insect) from the blood of man to drinking-water. In this endemic form elephantiasis begins with an attack of lymphangitis and erysipelatoid inflammation, with severe constitutional symptoms. The inflammatory effusion is but partially absorbed, and each successive attack leaves the tissues more swollen and hyperplastic. In temperate and cold countries the disease occurs sporadically, with slight or no constitutional symptoms, and its severe forms are rare. The same condition of the tissues, slight or moderate, or occasionally severe, may arise from obstruction of the lymphatics from any cause, such as may occur after repeated attacks of erysipelas, after removal of lymphatic glands, or from mechanic pressure of new growths. Frequently the condition appears gradually without recognized cause, and is occasionally congenital. The anatomic changes are most marked in the upper parts of the subcutaneous tissues, and vary from slight thickening in mild cases to an enormous thickening and hyperplasia in the severe forms, in which the tissue is composed of dense white fibrous bands and networks, interspersed with which are soft gelatiniform fibers, cells, and nuclei. The deeper part of the superficial fascia becomes a loose, yellowish, dropsical tissue containing a few fibrous bands and many large veins and lymphatics. Blood-vessels, lymphatics, muscular aponeurosis, and nerves are enlarged and thickened. The bones are often hypertrophied and rough, and the muscles may undergo fibrofatty changes. The derma is also thickened and fibrous, and there may be secondary hypertrophy and exfoliation of the epidermis. Nodular growths may thus form in the skin. The lymphatic glands are enlarged, dense, and fibrous. **Lymph-tumors** and **lymph-scrotum** are forms of elephantiasis in which the connective-tissue hypertrophy is comparatively slight, but in which there is irregular enlargement of the lymph-vessels and -spaces, which may appear on the surface as minute or larger varicosities, which on rupture discharge a serous or milky fluid. **Persistent edema** of the face following recurrent erysipelas is an allied condition. The changes of the skin in **acromegaly** may be similar to those in elephantiasis, but are usually more uniform and symmetric, and the growth of hair is everywhere increased.

¹ Allbutt's *Syst. of Med.*, iii.

INFLAMMATIONS.

INFECTIOUS INFLAMMATIONS.

BACTERIAL DISEASES.

In the **exanthemata** (*morbilli*, *scarlatina*, *variola*, and *varicella*) the skin lesions are undoubtedly due to the action of the poison circulating in the blood upon the blood-vessels of the skin, causing either a disturbance of the vasomotor apparatus or a progressive disturbance of the nutrition of the tissues. To this Unna¹ adds the primary action of the poison on the epidermic structures, which is indicated by general and mild or localized and serious disturbances of nutrition. He considers true inflammatory changes absent, or secondary and unessential, stating that desquamation results not from separation of the horny cells by an exudate, but from primary changes in the epidermis. In scarlatina he finds these changes independent of congestive phenomena.

The anatomic changes in **measles** include an arterial and venous congestion with edema of the corium. In the macular or but slightly papular eruption there is little or no cellular infiltration, and postmortem examination may show no changes, although Unna states that in thick sections properly stained (with acid orcein) dilated lymph-spaces and lymph-vessels, and marked edema of the fat-lobules about the follicles, coil-glands, and muscles, can always be demonstrated. In the larger papules there is some infiltration of leukocytes about the vessels and glands and in the papillary body. Small hemorrhages may occur in the derma and hypoderm. In severe cases there may be colloid changes and necrosis of the epithelium.

In the lesions of **scarlatina** there are a paralytic dilatation and intense congestion of all the blood-vessels of the skin, with edema, some transudation of leukocytes and of blood-pigment, and occasional small hemorrhages. Most authors describe a rapid proliferation of the rete-cells and a separation of the horny cells by an inflammatory exudate, leading to desquamation. Unna (see above) states that the edema, both of the corium and of the epithelium, is entirely parenchymatous, and that there is no dilatation of the interstitial spaces or of the lymph-spaces or lymph-vessels. He also finds but few leukocytes in the tissues (except in infants), and no mitotic changes in the rete before the stage of desquamation. The minute deep-red papules seen at the beginning of the exanthem are probably localized areas of intense congestion, and are not necessarily connected with follicles. The vesicles and bullæ occasionally seen in scarlatina have received no satisfactory histologic investigation.

In the skin lesions of **variola** the histologic changes begin with circumscribed hyperemia of the papillæ and exudation into the rete. The cells of the rete become swollen, undergo colliquative degeneration, and are more or less separated by the effusion or compressed into a sort of filamentous network which connects the raised portions of the epidermis with the papillæ beneath. The multilocular vesicle thus formed grows gradually at the periphery, where serum exudes usually in greater quantities than in the center, which is consequently lower than the border. The umbilication of the vesicle is not dependent upon the presence of a follicle or gland. The

¹ *The Histopathology of the Diseases of the Skin*, translated by Norman Walker, Edinburgh and New York, 1896.

roof of the vesicle is formed in the center by the horny layer, and on the sides by degenerating rete-cells. The floor is formed of denuded papillæ and the remains of the interpapillary processes of the rete. As the vesicle gradually changes into a pustule, the pus-cells, present in small numbers from the beginning, increase numerically, the network of shreds and bands breaks down, and a crust is formed, beneath which resolution and healing take place. There may be infiltration and circumscribed necrosis in the upper layers of the corium, resulting in typical scars (pock-marks). Destruction of the epidermis alone leaves no scars.

The vesicles of **varicella** may resemble closely those of variola, but are usually much more superficial and more rapidly formed; suppuration and scarring are unusual. Unna states that the peculiar form of cell degeneration which he calls "ballooning colliquation" is best seen and studied in varicella (and in zoster). Gilchrist¹ has described the multinuclear cells found in the vesicles of varicella (and of zoster), and has shown the difference between them and the protozoa forms with which they have been confused.

The vesicles of *vaccinia* correspond in structure to those of variola. The many and varied *vaccination rashes*, described after vaccination, are forms of dermatitis due to secondary or mixed infection, or other accidental causes.

Erysipelas is an inflammation of the skin, produced by the infection of a wound or abrasion of the skin or mucous membrane with the streptococcus of Fehleisen, which is closely related to, if not identical with, *Streptococcus pyogenes*. In some individuals, and especially those affected by chronic skin diseases, recurrences are common, local conditions favoring reinfection. The streptococci are found in both the derma and subcutaneous tissue, chiefly in the lymphatics and lymph-spaces. The local anatomic changes, most marked in the deeper layers of the corium and in the hypoderm, are: A serofibrinous exudate which distends the lymph-vessels and lymph-spaces, produces the characteristic firm edema, penetrates the hair-follicles, and sometimes passes between the rete-cells to form bullæ; cellular infiltration, most marked about the vessels; swelling, degeneration, and destruction of connective tissue and elastic fibers; granular and colliquative degeneration of rete-cells; and other manifestations of inflammation which may be severe enough to produce gangrene. The extension of the process is through the lymphatics.

Erysipeloid is an inflammation resembling erysipelas in type, but is subacute and very slow in extension. It is due to a special filamentous micro-organism, described by Rosenbach, and is found chiefly on the fingers and hands of butchers, cooks, dealers in hides, etc.

Impetigo and ecthyma are due to infection of the skin with pus-cocci. The conditions are found most frequently in children whose hygienic surroundings are poor or whose tissues are not well nourished. The old division of impetigo into *impetigo simplex* and *impetigo contagiosa* is unwarranted from the standpoint of etiology. The impetigo-pustule is superficially seated in the derma, is accompanied by but slight infiltration, and is not destructive in its tendencies. Uncomplicated cases leave no scars. *Ecthyma* differs from impetigo in degree only. The pustules are larger and seated upon an infiltration of deeper tissues. Pigmentation frequently results, but scarring is exceptional.

¹ *Johns Hopkins Hosp. Rep.*, i.

Folliculitis due to pus infection may occur in varying degrees of severity on any part of the body. Worthy of separate mention is *conglomerate suppurative perifolliculitis*, a rare disorder which occurs in circumscribed, elevated plaques, suggesting in appearance a flat carbuncle. The process involves follicles, perifollicular tissue, and glands, and may go deeper and become phlegmonous; or in chronic cases may result in a papillomatous growth. Besnier and Doyon describe five varieties of this disorder. In several cases Sabouraud and others have found the trichophyton.

Sycosis (*sycosis vulgaris*; *coccogenous sycosis*; "nonparasitic sycosis") is an inflammation of the hair-follicle and perifollicular tissue, due to infection with organisms probably identical with pus-cocci. The follicles, their sheaths, the hair-roots and sheaths, the perifollicular tissue, and occasionally the sebaceous glands, may be partially or completely destroyed, but the hair-papillæ usually escape, so that permanent alopecia and scarring are rare. Certain forms of sycosis, described as *lupoid sycosis*, *ulerythema sycosiforme*, etc., are more destructive, and are invariably followed by permanent alopecia and scar-tissue. Further investigation may prove these severe cases to be distinct etiologically from other forms of sycosis (see Folliculitis Decalvans).

Furuncle (*furunculus*; *boil*) is an acute inflammation of a hair-follicle and its sebaceous gland, and of a circumscribed area of connective tissue surrounding them. The immediate cause is an infection through the follicle with one or more of the pus-cocci, usually the *Staphylococcus aureus*. As a rule, the process is so acute and intense that a central area undergoes necrosis and is thrown off as a slough. Occasionally the process is less intense and no central slough or "core" is formed, thus producing the "blind boil." Predisposing causes to furuncles are found in many conditions, general or local, which lead to a lower vitality of the tissues, and in circumstances of occupation and habit which favor penetration of the follicle by the cocci.

Carbuncle (*carbunculus*; *benign anthrax*) in its origin is probably identical with furunculus, and in its later stages may be likened in appearance to a group of furuncles closely set together. It is a much less frequent disease than furuncle, and occurs chiefly in middle-aged and old people. The process differs from that of furuncles in that it spreads in the subcutaneous tissue, from which it extends upward, according to Warren, along the fat-columns, producing new foci of suppuration and of necrosis in the overlying skin. The necrotic areas slough away, forming numerous exits for the inflammatory products.

Anthrax (*malignant pustule*), as it affects the skin, is a carbuncular inflammation produced by inoculation of the skin with the *Bacillus anthracis*. The source of infection is found in horses, cattle, and sheep suffering from the disease, or in the hides or secretions of such animals. The early lesion is a papule or small furuncle, on the surface of which appear vesicles, bullæ, or pustules. If a general infection does not prove rapidly fatal, crusts form over these lesions, which are soon transformed into a gangrenous slough. Occasionally a diffuse extensive edema occurs instead of the above lesions. The anatomic changes are those of acute inflammation, followed by sero-fibrinous exudation and central necrosis. The cellular infiltration of the deeper layers may be slight or dense, but the bacilli are found chiefly in the papillary layer and in the rete.

Glanders (*equinia*; *farcy*) may originate in the skin as a result of infec-

tion with the *Bacillus mallei*. The skin lesions take the form of papules, nodules, vesicles, bullæ, variola-like pustules, or of deeper-seated phlegmonous and erysipelatoid inflammation. The early lesions may coalesce to form irregular, superficial or deep, sloughing, gangrenous patches. The lymphatic vessels and glands enlarge to form the nodules known as "farcy-buds," which break down and form indolent ulcers. The histologic changes, especially of the chronic ulcers, suggest those of tuberculosis, though giant cells are uncommon. The nodules show a dense accumulation of embryonic cells in the deeper layers of the corium; the vesicles are formed beneath the rete, the entire epidermis being raised and thinned. The bacilli are easily demonstrated in the various lesions.

Oriental furuncle (*Delhi boil*; *Aleppo evil*; *Biskra bouton*; *tropical ulcer*, etc.) is a chronic local contagious disease of some of the hot countries of Asia and Africa. The lesion begins as a papule which assumes the character of a small furuncle, ulcerates, and on healing leaves a depressed bluish-white scar. The disease is unquestionably contagious and infectious, and due to a micro-organism, the exact nature of which is not yet agreed upon. Histologically the primary papule closely resembles a lupus tubercle.



FIG. 361.—Lupus of the nose (vertical section): *a*, epidermis; *b*, normal corium; *c, c*, lupus-nodules (after Kaposi).

Tropical phagedenic ulcer (*phagedæna tropica*, etc.) is a rapidly extending gangrenous ulceration peculiar to certain hot countries, and which follows any accidental lesion of the skin. Boinet believes the disease is due to a micro-organism found in the mud and waters of infected districts.

Rhinoscleroma, a rare skin affection seldom seen outside of Austria, was formerly supposed to be a manifestation of syphilis, but is now known to be a distinct disease due to an encapsulated bacillus, first demonstrated by Frisch, which is a form of the *Bacillus mucosus capsulatus*. The histologic structure is that of a chronic inflammatory granuloma, the wide meshes formed by firm connective-tissue bundles being densely packed with small round cells. Mibelli further describes two types of cells which he considers characteristic of the process. The first, in which the bacilli are found, are more numerous than the second, are large, with reticulated protoplasm and small nucleus, and so edematous that they stain with great difficulty. The second have a colloid or hyaline appearance, are not numerous, and do not contain bacilli. He thinks these types are produced, not by cell degeneration, but by the presence of a mucous substance produced by the bacilli.

Tuberculosis of the Skin.—The labors of Koch, Baumgarten, Dou-

trelepont, and others have demonstrated the tuberculous nature of a number of dermatoses formerly considered distinct diseases. There exists a still larger number of skin affections the exact relation of which to tuberculosis is not yet determined. These have been variously classified as tuberculides, scrofulides, dermatoses of scrofulous subjects, and paratuberculides, and will be considered at the close of the section. The four following varieties of tuberculosis cutis are now generally recognized as due to direct or indirect inoculation with the tubercle bacillus: *Lupus vulgaris*, *tuberculosis verrucosa*, *tuberculosis cutis vera (tuberculosis orificialis)*, and *scrofuloderma*. In each of these four varieties the tubercle bacillus has been demonstrated in the tissues and has been satisfactorily cultivated. Animals inoculated with these tissues become tuberculous. It is true that inoculations have not reproduced the same type of cutaneous disease in the animals inoculated, and the last link in the chain of evidence is wanting, owing, undoubtedly, to the fact that the animals experimented upon are not susceptible to these forms of cutaneous tuberculosis. Though control-experiments producing the different forms of cutaneous tuberculosis are wanting, clinical facts are rapidly accumulating to show that tuberculosis of the skin results in the great majority of cases from direct inoculation with tuberculous virus. What other factors than the virus itself are present, to determine in each case the special form of the disease, is not known. The orificial ulcers are found only in subjects of tuberculosis of the internal organs, and are undoubtedly due to auto-infection from secretions which pass over the affected surface. There is abundant clinical evidence to show that tuberculosis verrucosa results from direct inoculation. Since Riehl and Paltouf called attention to this form of the disease, it has been observed frequently in individuals whose hands come in close contact with animal tissues. It has been studied in those engaged in postmortem operations or in the dissecting-room, in butchers, dealers in hides, and in others exposed to direct inoculation with tuberculous virus. A number of well-authenticated cases are on record in which individuals have acquired verrucous tuberculosis of the hands as a result of handling handkerchiefs and other articles soiled with the sputum of tuberculous patients. Moreover, this form of the disease may be followed by general tuberculosis. Pfeiffer reports a case in which death from phthisis occurred two years after such infection. Scrofulodermas frequently develop along the lymphatics leading from these verrucous growths, and true lupous nodules are also seen along the same route of infection, thus illustrating the association and interchangeability of the different forms of the disease. Among many cases of direct infection may be mentioned the 17 cases of Dubreuilh, following circumcision, in which the ritual operator, a consumptive, applied his lips to the wound. *Lupus vulgaris* usually begins in early childhood, and evidences of direct infection are not so numerous, but have been clearly established in a number of reported cases. Lupus may result also from indirect inoculation of the skin with secretion from deeper-seated lesions, and is thus seen along the lymphatics leading from a tuberculous gland or bone, the intervening tissues being unaffected. Lupus-nodules are also seen in the scars following tuberculous ulcers, and along the edges of a tuberculous fistula. Leloir reported 312 cases of lupus, of which 32 were preceded by tuberculosis of the glands, 41 by scrofuloderma, and 29 by tuberculosis of the bones and joints. The proportion of cases of cutaneous tuberculosis in which phthisis coexists varies, according

to different authors, from 10 to 60 per cent. The influence of heredity upon tuberculosis of the skin (as of other organs of the body) is not known. Congenital tuberculosis is practically unknown, and while the child may inherit feeble powers of resistance, infection probably occurs rarely (if ever) before birth.

The *histologic structure* of cutaneous tuberculosis corresponds with that of the disease in other organs. It is a granulation-tissue, showing in its earliest stages a delicate reticulum of connective-tissue fibers, embedded in which are leukocytes, lymphoid cells, and proliferating connective-tissue cells. Later are seen the large epithelioid cells with thin, large, clear nuclei, and there finally forms the typical tubercle with the giant cell of Langhans in the center, surrounded by the two zones of epithelioid and round cells. In the early stages the nodule is about the size of a millet-seed, is fairly sharply defined, and is limited to the corium. The process extends to the

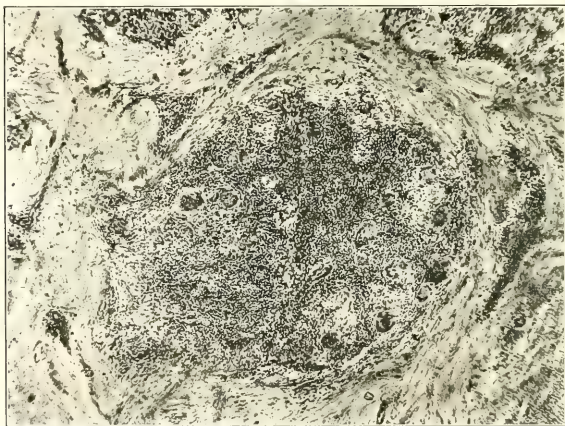


FIG. 362.—Tuberculosis cutis verrucosa. Tubercular nodule containing numerous giant cells and surrounded by dense connective tissue. From a photomicrograph (author's case; Dr. Rickett's preparation).

epithelium and subcutaneous tissue, either by the formation of new nodules or by a diffuse infiltration. No new vessels form in the nodule, and the old ones become obliterated, resulting in a coagulation necrosis, or cheesy degeneration, involving both the cells and intercellular substance. Since the histologic structure of the tubercle is found to a greater or less degree in all the granulomas, the one pathognomonic feature of tuberculosis cutis is the tubercle bacillus, which is found in all parts of the nodule, but chiefly in the giant cells.

In *lupus vulgaris* the main histologic features are those of slowly developing, persistent tuberculosis in other organs. Giant cells are numerous and infiltration of round cells is marked, but epithelioid cells are few. Bacilli are difficult of demonstration.¹ The nodule forms in the lower part

¹ By pressing a soft nodule between slides and staining, as in cover-glass preparations, a few bacilli can usually be found.

of the corium, and extends by the formation of new foci and by an irregular diffuse infiltration to the tissues above and below. Slow absorption of the cell infiltration may occur, leaving atrophic scars, but more frequently disappearance of the infiltration is accompanied by some connective-tissue proliferation, producing dense, irregular, scar-like tissue, in which can usually be found a few remaining nodules—*lupus scléreux*. The connective-tissue hyperplasia may be excessive, producing the various degrees of elephantiasis frequently seen in *lupus*. The nodules may break down and form ulcers, but this is not common unless the result of secondary pus infection, and the process is seemingly not true necrosis. The glands and follicles undergo atrophy, disappearing wholly or in part, or they may be the starting points of hyperplastic formations. The acini of the sebaceous glands are sometimes so packed with epithelial cells as to suggest the cell-nests of epithelioma. The process may involve cartilage and bone. The epithelium is involved secondarily, often early in the process, the rete-cells showing proliferation, cloudy swelling, and reticular degeneration. All the layers may be thinned, atrophied, and desquamating, or they may be entirely destroyed—*lupus exulcerans*; or there may be great increase in the size of the rete-pegs and of the papilla—*lupus hypertrophicus*, *lupus papillosus*—with frequently a corresponding thickening of the horny layer—*lupus verrucosus*. This marked hypertrophy of the epithelium may result in the formation of true epithelioma, which usually runs a rapid and destructive course.

In *tuberculosis cutis verrucosa* (*verruca necrogenica*) the process is practically that of *lupus verrucosus*. There is enormous thickening of the papillary and epidermal layers, with deep prolongations of the rete, and even of the horny layer, to fill the interpapillary spaces. Pus infection and secondary inflammatory changes are not uncommon. The bacillus is somewhat more abundant than in *lupus*.

In *tuberculosis cutis vera* the number of bacilli present is larger, and the process is that of acute miliary tuberculosis in other organs. Nodules form deep in the corium, and the process extends by the rapid formation of new foci. Destructive processes go on with equal rapidity to form the characteristic superficial ulcer.

In *scrofuloderma* the tuberculous formation begins in the subcutaneous tissue in or about the lymphatic glands or vessels. The process is subacute, but results in necrosis, which may remain superficial or may burrow deeply, even to the bone. The skin eventually becomes involved in a subacute inflammation, and is destroyed, producing the typical ulcer with soft, ragged, and often extensively undermined, edges. The number of bacilli present varies, but is greater than in *lupus* and less than in *tuberculosis cutis vera*.

Under the titles **dermatoses of the scrofulous** (Hyde¹), **tuberculides** (Darier²), **scrofulides**, **paratuberculides** (Johnston³), etc., have been classed a number of dermatoses and cutaneous phenomena which occur chiefly or solely in tuberculous individuals, and which are due apparently not to direct or indirect inoculation with the tubercle bacillus, but to toxins arising in distant tuberculous foci. Of the many dermatoses suggested in this connection, a few only are generally acknowledged as belonging in this category. They are all rare disorders.

Lichen scrofulosorum (*lichen scrofulosus*) was first described by Kaposi,

¹ *Trans. Third Cong. of Derm.*, London, 1896.

² *Ann. de Derm. et de Syph.*, Dec., 1896.

³ *Am. Jour. Med. Sci.*, Nov., 1897.

who found in the histologic structure a round-cell infiltration occupying the hair-follicles and immediately surrounding tissues, including the sebaceous glands. More recently Jacobi, Sack, and Darier have found in the perifollicular tissue lesions practically identical in structure with the nodule of tuberculosis. Bacilli have not been satisfactorily demonstrated in the lesions, however; nor have inoculation experiments proved successful.

Acne cachecticorum (*acne scrofulosorum*) occurs frequently in the tuberculous. The lesions are more extensive and persistent than in common acne, and usually necrose in the center, leaving a scar, but they do not show tuberculous structure. Certain forms of *folliculitis*, including the *large pustular scrofulide* and *small pustular scrofulide*, are sometimes present in the tuberculous. They may be due, as suggested above, to toxins or to pus infection on a peculiar soil. The *pigmentary tuberculide* corresponds to pigment anomalies found in other forms of cachexia. The possible relation of lupus erythematosus and erythema induratum to tuberculosis is considered in connection with these disorders.

Leprosy.—Leprosy belongs to the class of infectious granulomas of which tuberculosis and syphilis are the most conspicuous members. The leprosy

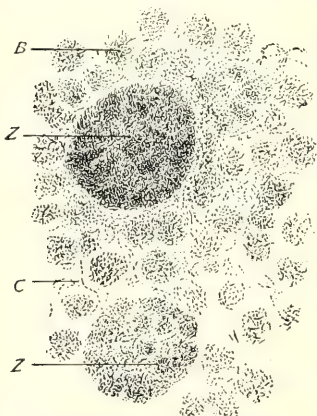


FIG. 363.—Bacilli shown in a section of the tongue in a case of tubercular leprosy. The bacilli are extracellular: B, bacilli in groups; Z, Z, zoöglear masses, large rounded masses of bacilli; C, bacilli in chains. $\times 600$ (Leloir).

nodules of the skin contain the bacilli in large numbers, and it is probable that the lesions of the skin are due in large part to the direct presence of the bacilli and in part to toxins. For convenience, leprosy has been divided into *nodular*, *macular*, or *anesthetic*, and *mixed* forms. These different forms are hardly entitled to consideration as distinct types of the disease, for in the great majority of cases the types are mixed, and show sooner or later both nodules and anesthetic macules. The nodules usually appear first in characteristic groups on the face and terminal joints of the extremities, but later may involve any portion of the skin or mucous membrane.

The **nodule** of leprosy is made up of granulation-tissue similar to that of tuberculosis and of syphilis.

There are, however, besides the usual lymphoid and epithelioid cells, other larger granular cells, which contain large vacuoles and are known as *lepra-cells*. Giant cells are present, but are not so typical as in tuberculous tissue. The new tissue is less vascular than in tuberculosis or syphilis, and both the formative and retrograde changes are slower. The infiltration begins in the corium, about the vessels, glands, and follicles, from which it spreads, in nodular or diffuse form, to involve the entire depth of the corium and portions of the subcutaneous tissue. The vessel-walls are greatly thickened and their lumen narrowed. The glands and follicles are involved early in a hyperplasia, but eventually are destroyed.

In older lesions the papillæ are obliterated. The epidermis is involved secondarily, and may be exfoliating, or thinned and atrophied, or may be destroyed, the necrosis resulting in an ulcer. As a result of secondary infection the nodule may be surmounted by a vesicle or pustule.

Bacilli are most numerous in recent, but fully developed, nodules, in which, on section, they may be found in globular masses made up almost wholly of bacilli. They are found also freely scattered through the tissues. Thoma thinks they extend largely through the lymphatics. There has been much discussion as to the exact histologic position of the *lepra bacillus*. Hansen and Looft, and the majority of other observers, have found the bacilli chiefly in the *lepra*-cells. Recently Unna, Bergengmen, and Kant-hack have brought forward strong evidence to show that the bacilli are found chiefly, if not solely, in the lymphatics.

In **macular and anesthetic leprosy** Hansen and Looft state that "the macules are, like the nodules, leprous infiltrations of the cutis, consisting of round, epithelioid, and spindle-cells, the latter being more numerous the greater the age of the nodule. The infiltrations appear to proceed from the vessels. *Lepra* bacilli are always present, but are most numerous in the young macules. In the young, not as yet anesthetic macules the nerve-twigs appear unchanged; in the older ones they are usually affected." According to Thoma, the nerve-changes begin in the small peripheral nerves and extend centripetally along the perineurium and endoneurium. Cells and bacilli are found within the external sheath and between the nerve-fibers, which gradually atrophy and disappear, owing to the mechanic pressure produced by the new-formed connective tissue. The latter may produce great increase in the size of the nerves. During the early changes the irritation or the nerve-fibers by pressure is manifested in pain and hyperesthesia. With atrophy of nerve-fibers come corresponding areas of anesthesia.

Hansen and Looft state that in both nodular and macular leprosy the neoplasm may entirely disappear; that "the bacilli in leprous products break up into granules which finally disappear, and there remains of the leprous products only a scar in which nothing leprous can be recognized. Occasionally this takes place in all the affected parts and there remains only a widespread anesthesia, the result of the nerve affection, and in the maculo-anesthetic form this is the regular termination of the disease. In both cases the leprosy is completely healed." Complete recovery from leprosy has been reported in but few cases. The process may remain stationary for years, the majority of patients dying of intercurrent affections. In *lepra mutilans* the fingers and toes and successive joints of the extremities slough off as the result of atrophy or ulceration. Ulceration may be deep and extensive, laying bare the deep-seated structures, even to the bone, over large areas. In such cases a fatal termination results from exhaustion or septicemia.

Syphilis.—Though Lustgarten, Doutrelepoint, and others have described a bacillus found not only in the chancre, but also in the later cutaneous lesions of syphilis, the pathogenic import of this micro-organism is not yet settled, and though syphilis is unquestionably an infectious disease, the nature of its infecting virus is still undetermined.

Histologically all cutaneous syphilitic lesions, including chancre, show the same structure and processes, varying only in extent, intensity, and

in minor features due to the accident of location and surroundings. The two chronic processes which are always present in varying degrees are hyperemia and a more or less dense infiltration, chiefly about the vessels, of lymphoid cells. Endothelial proliferation is usual. The histologic changes cannot be considered pathognomonic. In many of the papular, nodular, and gummatous lesions giant cells are found, and the microscopic appearances are practically those of tuberculosis. Involution of syphilitic proliferations in all their forms is accomplished either by fatty degeneration and absorption of the cells or by necrosis and ulceration. The cells are not capable of organizing new tissue. According to Jullien, the three characteristic features of all syphilides are the cell infiltration; the inevitable destruction of this infiltrate, the cells of which are incapable of organization; and the centrifugal development and retrogression of the lesion.

In the **macular syphilide** there may be simply hyperemia, stasis, and effusion of serum, with slight cell infiltration about the vessels. The process is superficial, chiefly in the papillary layer, and is usually circumscribed. The superficial vessels are dilated and show endothelial and perithelial proliferation. There is often slight cell accumulation about the glands and follicles. The epithelium of the coil-glands may be swollen. In the more or less urticarial type of the macular syphilide there is, in addition, an edema of the upper part of the cutis and of the epidermis. In older and thickened macules the structure gradually approaches that of the papule.

In the several forms of the **papular syphilide** the process is most pronounced in the papillary layer and about the vessels, but involves also the deeper portions of the corium. The perifollicular and perivascular lymph-spaces are more densely packed with the lymphoid cells than in the macules. Epithelioid and new connective-tissue cells are present in smaller number, as well as a few giant cells. Unna describes the new growth as made up chiefly of plasma-cells of different sizes. As compared with the lupus-nodule, he finds in the papular syphilide a greater number of incomplete giant cells, a different arrangement of the plasma-cells, and a larger number of spindle-cells, together with better preservation of the fibrous tissue along the lymphatics. He also describes an increase in fibrous tissue coincidently with the cellular growth, giving the characteristic firmness to the papules. The number of cells in the papillary portion may be so great as to obscure the normal structure, or to efface the dividing line between the papillæ and epidermis. The blood-vessels are dilated and show proliferation of the endothelium and perithelium. The cells lining the coil-glands are swollen and may multiply sufficiently to block the canal, or often to obliterate it. The hair-follicle may be the center of the infiltrate, which may penetrate the root-sheaths, hair-papillæ, and sebaceous glands, possibly obliterating these structures. Pigment is sometimes found in the basal layer of the rete and also in the corium. The connective tissue of the corium is usually normal, and the majority of papular syphilides are absorbed, leaving no scar. In persistent and deeper papules there may be destruction of normal tissue, leaving atrophic scars. The epidermis is involved secondarily, and may be thinned and atrophied, or thickened and exfoliating. On the palms and soles, where the integument is so closely attached to the deeper tissues, mechanic pressure causes the papule to form a broader, flatter lesion than on other parts of the body. In these regions, and occasionally in others, a

persistent thickening and exfoliation, due probably to a secondary inflammatory process, may continue long after all evidences of the original cell infiltration have disappeared. In regions such as the anal and genital, where lesions are subjected to warmth, moisture, and friction, the larger papules of syphilis may form flat condylomas, in which the original histologic structure of the papule may be largely obscured by the secondary and extensive hypertrophy of the rete, which extends down between the papillæ in deep, broad processes, although over the apices of the papillæ it may be greatly thinned. There is also marked edema of the corium and rete, with dilatation of the lymph-spaces and leukocytic infiltration.

Vesicular and pustular lesions are seen rarely in syphilis, except as the result of accidental secondary infection, and usually in very young, in very old, or in cachectic subjects. These moist lesions form, as a rule, at the apices of papules, and may in some cases be due to an increased intensity and rapidity of the usual process. A pustule or superficial ulcer may result from the destruction of cells in the center of a papule. Many of the crusted papular syphilides owe their peculiar appearances largely to a seborrheal process.

The **nodular (tubercular) syphilide** is practically identical in structure with the papule, but is larger and lies deeper in the cutis. Unna states that the connective-tissue hyperplasia is in greater proportion than in the papule, that the fibers in the papillæ are much thickened, and that the blood-vessels and lymph-vessels are greatly dilated and their walls much thickened. The atrophic changes in the epidermis are secondary. The nodular syphilide is slower of evolution and more persistent than the papule, hence some destruction of the normal tissue is frequent, and disappearance of the nodule is commonly followed by an atrophic scar. There may be necrosis of the cells in the center of the nodule, resulting in the formation of a small ulcer. Like all syphilitic processes, the new growth may spread peripherally, followed from the center by degeneration and absorption or by necrosis and ulceration. The process is commonly circumscribed, but may be diffuse.

The **gumma** has the same structure and follows much the same course as the nodule described, but is larger, and situated chiefly in the subcutaneous tissue, involving the skin secondarily.

Frambesia (*yaws*) is an endemic and infectious disease of some tropical countries. It occurs most frequently among negroes. It has many analogies with syphilis, in that after a period of incubation a primary lesion appears at the site of inoculation and is followed, after a second period of incubation, by secondary general lesions of the skin, with usually some constitutional disturbance, and frequently a general adenopathy. A definite bacillus has been found and cultivated, and the disease produced in animals by inoculation with pure cultures. The clinical succession of erythemas, desquamation, papules, nodules, and ulcerating lesions also suggests an analogy to syphilis. The later and deeper lesions are usually fungoid in form, and, when the overlying crust is removed, may present an appearance resembling a cauliflower or raspberry. The disease may run an acute course of a few months or persist for several years. The lesions are usually limited to the upper parts of the cutis, and present the histologic characteristics of the other infectious granulomas.

Mycosis fungoides has been classed by most writers with sarcoma, as many of the tumors show a histologic structure very similar to that of the

round-cell sarcoma. The spontaneous involution of fully developed tumors, and the great rarity with which the disease attacks the internal organs, would seem to distinguish it from sarcoma, while the histologic structure of the earlier lesions leaves little doubt that the disease belongs to the infectious granulomas, and that the erythematous and infiltrated areas, which in the majority of cases precede for months or years the tumor formations, are early manifestations of a definite disease, and should not be confounded with other dermatoses. Histologic examination of early erythematous lesions shows all infiltration to be sharply limited to the papillary and subpapillary layers except about some of the deeper vessels, where the cells appear in the form of sheaths or "cuffs." Infiltration may be diffuse or more or less circumscribed and subdivided by normal connective-tissue bundles. Where the cells are most abundant they are supported by delicate connective tissue. The cells correspond in the main to the type of young connective-tissue cells, but there exists also a great diversity in form and size of cells, nuclei, and cell-fragments. Mitotic figures are frequent. The vessels are dilated, and there is some edema both of cutis and rete. The epidermal changes are secondary, the rete being thickened, sending down short, broad processes between the papillæ. Aside from edema and some cell degeneration, the rete shows in this stage small spaces filled with nuclear débris and leukocytes, or with collections of (apparently) connective-tissue cells described by most writers as "cell-nests."

In the later stages the cell multiplication seems to overcome cell destruction, the cells are more regular in form and size, and are often arranged in columns. The connective tissue supporting the cells is exceedingly fine and delicate. The epithelium usually recedes before the infiltration and becomes very thin and fine, often a mere line; but it may remain thickened and send deep prolongations into the group, suggesting the appearance of carcinoma. The stage of erythema and infiltration may last for years before the appearance of tumors, after which the disease usually pursues a rapidly fatal course. Fully developed tumors may undergo a spontaneous and complete involution, but eventually form fungoid and ulcerating masses, the patient dying usually from exhaustion or from sepsis.

The causes of the disease are not known. Several observers have found micro-organisms in the tissues, the significance of which has not been demonstrated. Secondary pus infection is common.

FUNGUS DISEASES.

Favus is due to the presence and development of a vegetable parasite, the *Achorion Schönleini*. The disease is usually transmitted from man to man, but may undoubtedly be derived from domestic animals which are subject to the disease. It is of slower development, less contagious, and of much less frequent occurrence than ringworm. Recent observers have tried to establish several clinical varieties of the disease and to demonstrate the plurality of the favus-fungus, but as yet all reports are conflicting, and conservative writers believe the various clinical, microscopic, and cultural appearances are due to the development, under varied circumstances, of the one fungus. The mycelia preponderate, and are for the most part moniliform or divided by transverse partitions into small cavities, many of which contain spores. The threads are frequently branched, and vary greatly in

length and in diameter, some of the finer ones having smooth borders and no partitions. The spores also vary greatly in size, and while some appear round or oval, the shape is usually oblong, polyhedral, or irregular. They

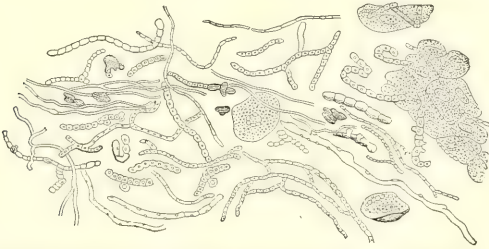


FIG. 364.—*Achorion Schönleinii* from the under surface of favic scutulum, showing various forms of mycelia and spores (Kaposi).

are most abundant at the ends of certain mycelial threads, but occur also either scattered or in groups between the mycelia. The most common site of the disease is in the hair and the hair-follicles, but other parts of the body are frequently affected.

The fungus grows between the horny layers of the epidermis, which it forces apart, and in typical development produces a cup-shaped, sulphur-yellow mass or *scutulum*, which is concave above and convex below. Unna states that the concavity of the free surface is due to the more rapid growth of the fungus at the periphery. When situated in the hair-follicle, the hair which penetrates the center of the crust may aid mechanically in preventing the upward growth of the mass. Regarding the exact point and mode of entrance of the spores into the hair, observers are not in accord. The fungus is most abundant in the hair and inner root-sheath, occupying the upper three-fourths of the follicle, but may be found in the shaft of the hair for a considerable distance from the scalp. In the nails the fungus is found between the horny layers of the nail-plate.¹ Long-continued pressure of the favus-masses on the



FIG. 365.—*Achorion* invading the root-sheaths and bulb of the hair (Kaposi).

¹For the method of preparing the fungus for examination, see note under Ringworm.

tissue below frequently results in atrophy of the hair-papilla, of the rete, and of the upper part of the corium, thus producing permanent alopecia and atrophic scarring. Scarring and alopecia are further caused by more or less inflammation which the fungus excites. Atrophy of the sebaceous glands with retention cysts of the hair-follicles and of the sweat-glands are described.

Tinea trichophytina (ringworm), **tinea circinata**, **tinea tonsurans**, and **tinea sycosis** (*hyphogenous sycosis*) are terms generally used to denote, respectively, ringworm of the body, of the scalp, and of the beard. The recent elaborate researches of Sabouraud¹ and others has demonstrated that these different forms of ringworm are produced by at least two distinct and unrelated forms of fungus—the *Microsporon Audouini*, or small-spored fungus; and the *trichophyton*, or large-spored fungus, of which several varieties are recognized. According to Sabouraud, in the microsporon the mycelia are all within the hair proper, and after dividing and subdividing terminate on the outer surface of the hair-shaft in fine filaments, at the extremity of which are the spores, which in this fungus are wholly external and are seen irregularly grouped or massed about the fol-

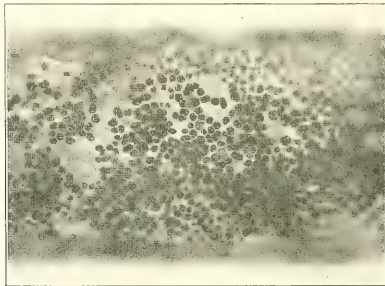


FIG. 366.—Portion of hair, showing *Microsporon Audouini*. $\times 680$. From a photomicrograph (author's case).

licular portion of the hair. The sheath of spores, in the form of a whitish or grayish coating, surround the hair for from a sixteenth to an eighth of an inch above the exit of the hair from the follicle, and may be seen by the unaided eye. The microsporon is the only fungus which is capable of a complete developmental cycle with sporulation on the human body, a fact that may account for its extreme contagiousness and resistance to treatment. The spores vary in diameter from 2 to 4 μ , the mycelium being slightly larger. The *trichophyton* is composed of spores varying in size from 3 to 6 μ . They may be oval, cuboid, or irregularly rounded, but are always arranged in lines or chains parallel with the axis of the hair;

¹ Sabouraud, *Les Trichophyties Humaines*, Paris, 1894, with Atlas; *Diagnostic et traitement de la pelade et des teignes de l'enfant*, Paris, 1895; *Trans. Third Internat. Cong. of Derm.*, discussions and papers by Sabouraud, Rosenbach, and Morris. Adamson, *Brit. Jour. of Derm.*, July, Aug., and Dec., 1895. Morris, *Practitioner*, Aug., 1895; *Ringworm—Pathology, Treatment, and Prophylaxis*, London, 1898. Fox and Blaxall, *Brit. Jour. of Derm.*, July, Aug., Sept., and Oct., 1896. Rosenbach, *Ueber die triferen eiternden Schimmelerkrankungen der Haut*, Wiesbaden, 1894. Roberts, *Jour. Path. and Bact.*, Aug., 1895. Bodin, *Des Teignes tondantes du cheval et leur inoculations humaines*, Paris, 1896. Mibelli, *Ann. de Derm. et de Syph.*, 1895.

in hairs which are densely packed with spores this arrangement of the latter in lines may be obscured in places. Mycelium is never found in the hair. Three chief varieties of the trichophyton are described according to the position of the spores within or without the hair: The *endothrix*, the *ectothrix*, and the *endo-ectothrix*. By the use of culture-experiments Sabouraud has produced a number of subvarieties, which, however, may be due largely or wholly to differences in media or circumstances of cultivation. Finally there are occasional forms which only the use of cultures will distinguish from favus. Of all cases of *tinea tonsurans* in children, the microsporon is responsible for 60 per cent. in Paris and for 90 per cent. in London, while in Italy, Germany, and Austria it is rarely seen. All of these fungi seem to have a definite geographic distribution, which would account for different results obtained by observers in different countries. In France the *endothrix*, like the microsporon, is found only in *tinea tonsurans* of children, if exception be made of the irregular, scaling, superficial patches which are

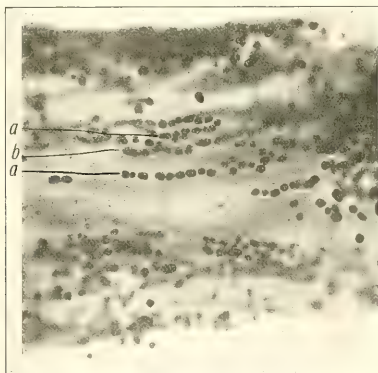


FIG. 367.—Portion of hair invaded by trichophyton, endo-ectothrix: *a, a*, chains of spores in focus; *b*, chain of spores lying deeper in the hair, and therefore not in focus. $\times 450$. From a photomicrograph (author's case).

transitory on the skin of children having *tinea tonsurans*. In London the microsporon has been found on the body, and even in kerion. The *ectothrix* and *endo-ectothrix* are derived directly or indirectly from domestic animals, and are found in all cases of ringworm of the body and of the beard, and in all suppurating forms of the disease, as sycosis and kerion.¹

¹ The hair may be placed at once between a slide and cover-glass in a 25 to 40 per cent. solution of potassium hydroxid. This quickly clears the hair for immediate examination, but also rapidly disintegrates it. The relative positions of hair and fungus are better preserved by the slower clearing of the hair in a 5 to 10 per cent. solution of potassium hydroxid, in which destructive action can be arrested at any time desired. The time required will vary from a few minutes to many hours, depending chiefly upon the strength of the hair. Several methods of staining the fungi have been tried with more or less success. The following method is recommended by Morris and Calhoun: The hair is washed in ether to remove the fatty material. It is then stained in a 5 per cent. solution of gentian-violet in 70 per cent. alcohol, or in a 5 per cent. solution of fuchsin in water with a little alcohol, or in a 2 per cent. solution of carbol-fuchsin. The microsporon stains in about five minutes, but the trichophyton requires about an hour, and should be heated over a spirit lamp for a few minutes. The stain is next fixed in iodine, decolorized in anilin oil, cleared in xylol, and mounted in xylol balsam.

Tinea circinata is due to the presence and development of the trichophyton in the deeper layers of the stratum corneum and upper part of the rete. The spores appear first, and are followed by the mycelium, which closely resembles that of favus, but is finer, less beaded, and much less abundant. The fungus grows and spreads centrifugally, forming the circinate lesions characteristic of ringworm. Its presence and activity produce a superficial and usually mild inflammation which is responsible for the varying clinical phenomena of the disease. The inflammation is most severe in regions that are constantly moist and warm (as in *eczema marginatum*); and it is severe also in tropical countries. The development of the fungus is modified by the peculiarities of the individual skin and by the circumstances of protection, heat, moisture, etc.

Tinea tonsurans is frequent in children, but rare in adults. It is contagious, and frequently occurs in epidemics. It is due to invasion of the

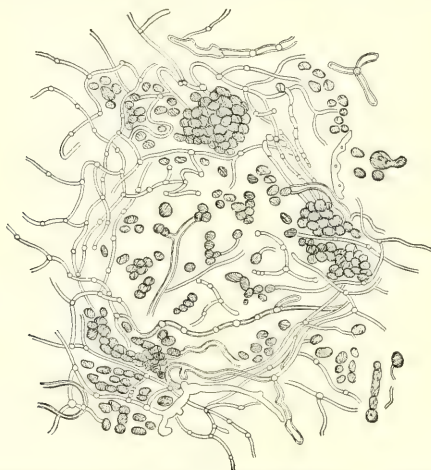


FIG. 368.—*Microsporon furfur*, fungus of pityriasis versicolor. $\times 700$ (Kaposi).

scalp, hairs, and follicles by the microsporon or by the endothrix. The exact point and mode of entrance of the fungus into the hair are not known, but the spores and a scanty mycelium are found in the follicle, bulb, and shaft of the hair, and in the scales on the surface of the scalp. Both root and shaft of the hair may be distorted and expanded by its mechanic division into many filaments, between which is seen the fungus. The hairs are, in consequence, brittle and usually broken off near the scalp, the ends presenting a brush-like appearance. The secondary inflammation of the surrounding tissue is usually slight; when severe, as in *kerion*, it is due to secondary infection or to the presence of a special form of ectothrix.

In **tinea sycosis** (*hyphogenous sycosis*; *parasitic sycosis*) the presence and growth of the ectothrix (or possibly of the endo-ectothrix) not only destroy the hair and loosen it from its follicle, but also excite a follicular

and perifollicular inflammation. Ullmann thinks the inflammatory process begins as a perifolliculitis, and is due to toxins produced by the fungus. Robinson thinks the process begins in the follicle, and thus accounts for early loosening of the hair. The intensity and extent of the inflammation vary greatly, and depend in part on the resisting power of the skin and other external influences, such as neglect, improper treatment, etc. Destruction of the follicle and sebaceous glands frequently occurs, and deeper tissue may be involved in the formation of small phlegmons. In some instances suppuration is undoubtedly due to secondary infection with pus-cocci.

Tinea imbricata (*Tokelau ringworm*, etc.) is a contagious disease of tropical countries, due to a vegetable parasite closely resembling the trichophyton. The fungus does not affect the hair-follicle, but is confined to the epidermis.

Tinea versicolor (*pityriasis versicolor*) is due to a vegetable fungus, the *Microsporon furfur*, which penetrates between the upper layers of the stratum corneum and produces a slight desquamation but no inflammation,



FIG. 369.—*Microsporon minutissimum* (No. 12 immersion) (Corlett).

and does not affect the hair-follicle. The disease is feebly contagious, and is usually limited to the protected portions of the body. The fungus consists of short threads and of oval, highly refractive spores, which are collected in clusters or irregular masses. The spores vary from 3 to 8 μ in diameter. The fungus is abundant in the scales, and is easily demonstrated by soaking the latter in a solution of potassium hydroxide.

Erythrasma is a slight furfuraceous disorder affecting regions which are warm and moist, and in which opposed surfaces come in contact, as in the axillæ and the groins. It is exceedingly chronic, and is supposedly due to a vegetable fungus, the *Microsporon minutissimum*, of which the spores and mycelia are but about one-third the size of those of the *Microsporon Audouini*. Other micro-organisms are found in the scales, however, and some observers believe the condition is due to bacteria.

Mycetoma (*Madura disease*; *Madura foot*; *fungous foot of India*) is a rare disease outside of India and a few other hot countries. There are two forms of mycetoma, the pale or yellow variety and the black

variety. The pale form is caused by a ray-fungus, *Actinomyces maduræ* of Vincent; it properly might be called the actinomycelial form. The black form is caused by a hyphomyces, which has been cultivated only once and by Wright¹ in the only American case of this form of mycetoma so far observed; this form might be called the hyphomycelial. In both forms similar lesions develop; the tissues of the foot, including the bones, are penetrated in all directions by tunnels and sinuses, in which are found fungous granules of yellowish or blackish color, depending on the kind of organism present. The black granules are much the larger. The yellow granules resemble fish-roe. In a few instances the hand has been the seat of the disease. Only 5 cases have been observed in America, 4² of the pale and 1 of the black or melanoid form (Wright). The yellow form of mycetoma differs from actinomycosis in being a chronic local process that rarely, if ever, causes secondary involvements.

Cutaneous actinomycosis may be primary, but it is more frequently secondary to deeper foci. The process does not differ histologically from

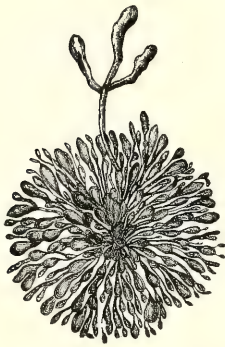


FIG. 370. — Actinomycetes-granule (Ponüick).

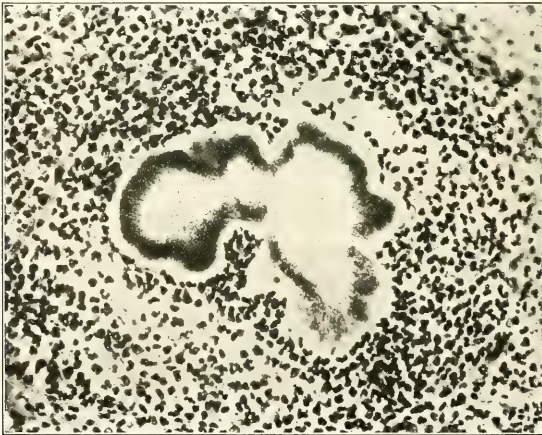


FIG. 371. — Mycetoma: fungus surrounded by a dense accumulation of leukocytes. $\times 300$. From a photomicrograph (Dr. Hyde's case).

actinomycosis elsewhere, and is recognized by the presence of the peculiar fungus-clusters.

¹ *Jour. Exper. Med.*, iii., 1898.

² Adami, Hyde, Pope and Lamb, Anoine and Lamb. For bibliography, see Anoine and Lamb, *Am. Jour. Med. Sci.*, 393, 1899.

Blastomycetic Dermatitis.—Blastomycetic infection of the skin has been reported by Buschke, Busse, Gilchrist,¹ Hyde, Bevan and Hektoen,² and others, including the writer.³

The disease begins as an inflammatory papule or pustule, and spreads slowly, during months or years, in the form usually of verrucous or crusted lesions, which cover small or large areas of the skin. The clinical picture

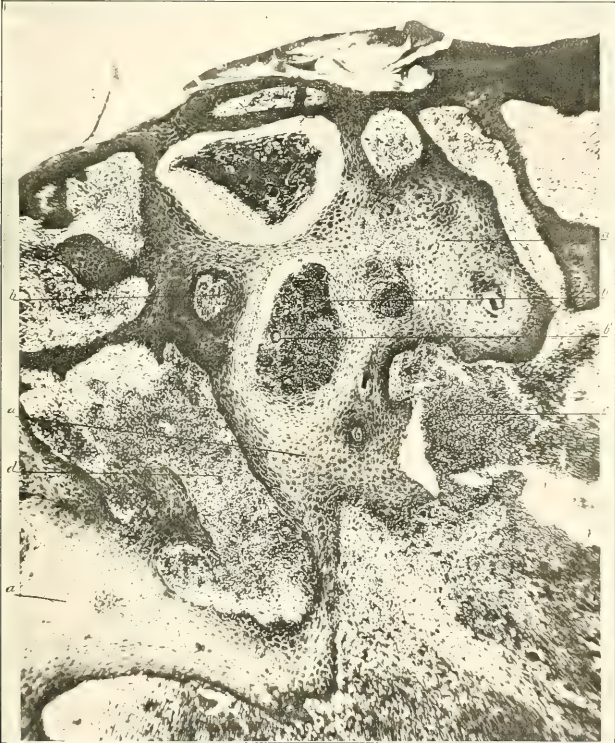


FIG. 372.—Blastomycetic dermatitis: low power: a, proliferated epithelium; b, miliary abscesses in the epithelium; b', giant cell; c, abscess in the cutis; d, cell infiltration of the cutis. From a photomicrograph (author's case).

in most cases resembles that of verrucous tuberculosis. The lesions, however, are more extensive and are usually multiple, occurring on more than one region of the body. In places the lesions have the appearance of super-

¹ *Johns Hopkins Hosp. Rep.*, i.; *Jour. Exper. Med.*, iii., 53.

² *Brit. Jour. Derm.*, Nov., 1899; *Jour. Exper. Med.*, iv., No. 3.

³ For a report of 6 cases, 2 by Hyde, 1 by Dyer, and 3 by the author, with bibliography to date, see *Trans. Am. Derm. Assoc.*, 1900, and *Jour. Cutan. and Gen.-Urin. Dis.*, Jan., 1901.

ficial papillary epithelioma. In one of the author's cases the disease was limited to the lower lip, where it produced a tumor-like swelling, which at first sight could easily have been taken for epithelioma. In every case, however, the clinical picture has been such as to suggest a disorder differing in one or more particulars from any hitherto recognized type of cutaneous disease.

Some lesions heal spontaneously, leaving thin or thick and elevated scars. All cases improve greatly under the internal administration of the iodid of potassium, some recovering completely, others recurring on withdrawal of the drug. Complete ablation has not been followed by recurrence.

Histologically the lesions bear a striking resemblance to those of verrucous tuberculosis or of superficial epithelioma, yet differ from both. Sec-

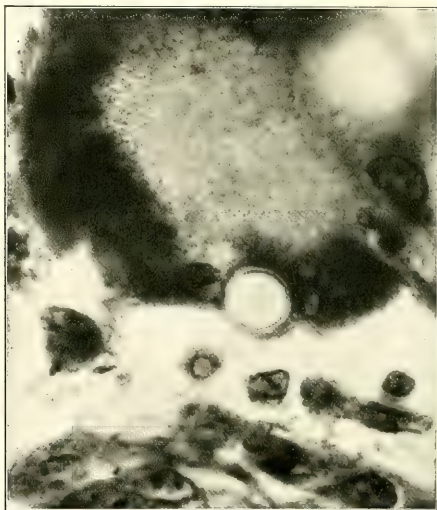


FIG. 373.—Blastomycetic dermatitis, showing a "vacuolated" blastomyces in the border of a giant cell. $\times 1200$. From a photomicrograph (author's case).

tions show a very uneven surface, marked by irregular papilliform projections, between which are corresponding depressions. On the surface are seen irregular masses of débris, consisting of pus, blood, and epithelial cells, and various bacteria. The horny layer varies greatly in thickness. In places it is destroyed; in others it extends in thickened masses between distorted papillæ.

The most pronounced changes, however, occur in the rete, which is everywhere the seat of excessive hyperplasia, producing branching downgrowths which vary greatly in size and shape. Polymorphonuclear leukocytes are scattered throughout the epithelium, both between and within the cells, and occur often in small collections which form the beginning of miliary abscesses. These abscesses are quite characteristic of the process,

and are found in all parts of the hyperplastic epithelium, in places breaking through to the surface. They contain leukocytes, nuclear fragments, detached epithelial cells, epithelial detritus, red blood-corpuscles, the organisms peculiar to the disease, and in most cases giant cells. The epithelial cells surrounding the abscesses are flattened mechanically, but appear to take no active part in the process. The epithelium is separated from the corium in most places by a distinct layer of columnar cells, in which mitoses are seen occasionally. The rete-cells in general are large and appear swollen, the prickles being very conspicuous and the intercellular spaces increased. Premature cornification, more or less complete, is seen in scattered individual cells, in groups of cells, and occasionally in isolated epithelial whorls. Single giant cells, surrounded by a few leukocytes, are sometimes seen in the epithelium, at some distance from the corium.

The corium is the seat of subacute, chronic, and occasionally of acute, inflammatory changes. Miliary abscesses occur, especially in acute lesions. The infiltration consists chiefly of leukocytes, endothelial cells, and plasma-cells, and is sometimes very dense. The number of mast-cells and giant cells varies in different cases. Tubercle-like nodules are found in some instances. In several cases numerous hyaline bodies were found. These bodies varied greatly in size, and occurred chiefly in plasma-cells, giant, and new connective-tissue cells.

The appendages of the skin apparently play but a passive part in the process.

The organisms characteristic of the disease are found in miliary abscesses, between the epithelial cells and in the corium, and are always surrounded by more or less evidence of inflammation. The giant cells usually contain one or more of the parasites. The number present in the tissue varies greatly. In some cases a dozen or more may be seen in a single field of the microscope, while in others they are found with difficulty. They are seen usually in pairs of unequal size, but occur also singly and in groups. They are readily seen in sections stained with hematoxylin and eosin or other common stains, but methylene-blue is best for showing the different parts of the organism. The simplest method of demonstrating the fungus is by placing fresh or hardened sections, or pus, in a strong solution of potassium hydroxid, or in equal parts of liquor potassæ and glycerin. The organisms then appear as doubly contoured, highly refractive bodies.

In stained sections the parasite is seen to be a round, oval, or slightly irregular body, having a well-defined, double-contoured, homogeneous capsule, which resists the prolonged action of strong alkalies and acids, and a finely or coarsely granular protoplasm, which is separated from the capsule by a clear space of varying width. The protoplasm often contains a clear vacuole, which varies greatly in size in different bodies. Mature organisms have a diameter of from 7 to 20 μ , though larger forms are seen occasionally, and smaller forms also occur.

Budding forms are found in all stages of development. The capsule and clear space are pushed out apparently by the protoplasm to form oval buds, which grow to about one-half the size of the mother-cell before separating from the latter. Organisms in pairs of unequal size are more common than budding forms.

Cultures of blastomyces are recorded in 8 of the cases so far reported. In the majority of them cultivation of the fungus has been successful only

after repeated attempts. Cultures have been obtained from the pus and from tissue. Associated with the blastomyces in some cases have been found various bacilli and cocci, none of which has been demonstrated to have any definite relation to the process. In 2 cases repeated inoculations of media with pus from one of the lesions gave rise to pure cultures of the blastomyces, showing that the organism was pyogenic.

Various media have been employed. Among the best are beerwort, agar, glycerin- and glucose-agar. The fungus grows readily at room-temperature, or at 35° C. In the majority of instances it would not grow as a strict anaërobe; milk was neither coagulated nor acidulated; gelatin was not liquefied; except in the case of the organism described by Buschke and Busse, no or little fermentation occurred in glucose-, lactose-, or saccharose-bouillon; and no indol was formed.

The gross appearance of the colonies, also the size, the rapidity and mode of growth, and the morphology of the organism, varied considerably in different cases. Variations due to the medium employed, to the age of the growth, and to other circumstances were noted in individual cases. Small buds and young organisms sometimes appear merely as highly refractive and doubly contoured, or as simple opaque, bodies, but in the older and larger forms the structure of the organism can be demonstrated readily. Multiplication occurs chiefly by budding, but in some media more or less perfect mycelium forms.

Inoculation tests have been largely unsuccessful, but in several instances subcutaneous injection of pure cultures of the blastomyces have resulted in the production of a local abscess or of an inflammatory granulation-tissue, from which the fungus could be recovered. The organisms in 3 cases¹ have been inoculated in animals with the production of tubercle-like nodules, or other inflammatory areas, in the lungs, kidneys, and other organs, from which the fungus has been recovered and cultivated.

The experimental researches of Lydia Rabinowitsch, Sanfelice, and other investigators have demonstrated that a number of yeasts are pathogenic for animals, producing growths of the type of an inflammatory granuloma. The variations in size and in some cultural and pathogenic properties of the organisms as described in different cases may be explained by the supposition that the disease under consideration may be produced by several varieties of the blastomyces.

An effort has been made by certain Italian investigators to establish a relationship between blastomyces and malignant tumors, but such a relationship is far from being satisfactorily demonstrated.

ANIMAL PARASITIC DISEASES.

Scabies is an inflammatory disease of the skin, of polymorphic symptoms, due to the *Acarus scabiei* or itch-mite. The female mite penetrates the horny layer and burrows in the rete and even to the upper portion of the corium, forming a curved or irregular furrow or *cuniculus*. In recent cases, before the furrow has been destroyed by inflammatory action, the mite can usually be found at the blind end of the furrow, where it appears as a white speck about the size of a pin-point. Behind her in the furrow are numerous ova and feces in the form of little black dots. Aside from the

¹ Gilchrist, Stokes; Hyde, Hektoen; Montgomery, Ricketts.

furrow, a variety of lesions are produced by the secondary inflammatory process induced by the presence of the mite and by the scratching.

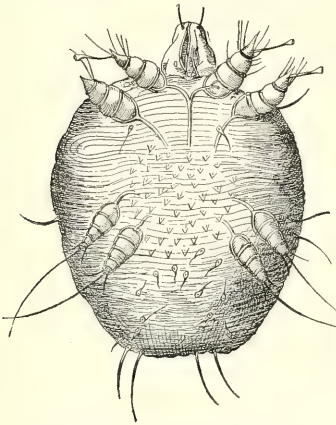


FIG. 374.—Female acarus (after Anderson).

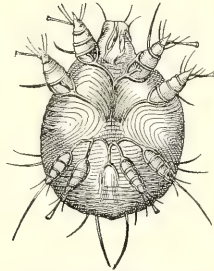


FIG. 375.—Male acarus (after Anderson).



FIG. 376.—Acarus folliculorum (after Küchenmeister).

The disease is contagious, but for the transference of the disease it is necessary that there be transplanted upon the skin either a colony of the



FIG. 377.—Body-louse (Küchenmeister).

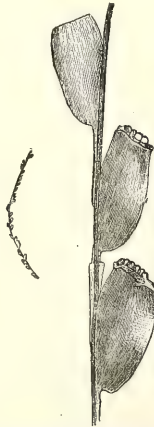


FIG. 378.—Nits of *Pediculus capitis* (after Kaposi).



FIG. 379.—Male *Pediculus capitis* (after Küchenmeister).

parasites, or at least one impregnated female. The full development of young acari from the eggs requires about three weeks.

The **Demodex folliculorum** is a microscopic parasite in the form of an elongated and jointed worm found upon the free surface of the integument, especially in parts where the sebaceous glands are large. It is found in the comedo plug, but is not known to have any pathologic significance.

Pediculosis is a contagious affection produced by the presence of lice upon the skin and hairs. The inflammatory phenomena result from the wounds produced by the insect and by scratching. There are three forms of the parasite, each of which commonly infects a different portion of the body.

In **pediculosis capitis** the presence of the parasite on the scalp excites inflammation in varying degrees. In severe cases there is marked exudation with the production of heavy crusts. There is frequently secondary infection, producing pustules and even furuncles or small abscesses. The parasite can usually be detected crawling on the scalp or among the hairs, while on the hairs, fastened to them by a chitinous sheath, may be seen the characteristic oval ova.

In **pediculosis corporis** the phenomena are wholly inflammatory, and due to traumatism. The insect inhabits the seams and coarse meshes of undergarments, which they leave only for the purpose of obtaining nutriment from the skin of their host, and hence are rarely found upon the free surface of the integument.

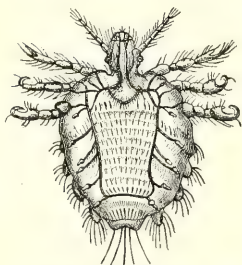


FIG. 380.—*Pediculus pubis* (after Schmarda).

Pediculosis pubis is usually limited to the genital region, though the parasite may invade other hairy parts of the body. The pubic louse is less active than the others, and can often be found grasping one or more hairs in its claws, while its head is buried deeply in a follicular orifice. The ova or nits are similar to those of the head-lice, but smaller, and are attached to the hair in the same

manner. The secondary inflammatory symptoms are usually much milder than those found in either of the other forms of pediculosis.

Filaria medinensis (*Guinea-worm*) is a parasite which gains access to the body through water containing the larvæ. The disease is rarely found outside of hot countries. The female worm, which alone invades the human body, is filiform, cylindric, and from 15 to 40 inches long, and about $\frac{1}{10}$ inch in diameter. The impregnated female is lodged in muscles or other tissues during the ten to fifteen months in which she is maturing, and then travels to the surface of the body, where she may be felt under the skin as a soft coil. Over this a vesicle or small bulla forms, and is followed by a small superficial ulcer, in the center of which is a small opening through which the worm protrudes her head or discharges her young, after which she emerges herself. If the worm aborts or is ruptured, and the young discharged into the tissue, abscess results, which may be followed by severe lymphangitis, gangrene, or septicemia.

Two cases of **protozoan infection** of the skin and other organs are reported by Rixford and Gilchrist. In both, the clinical symptoms and the histologic lesions were those of tuberculosis of the skin. One corresponded to the verrucous type of tuberculosis, the other to the more acute

miliary type. No tubercle bacilli were found in the lesions, however, but protozoa were present in large numbers. No cultures could be obtained, and inoculation experiments were unsatisfactory.

A few other parasites may infect occasionally the human skin and inflict wounds of greater or less degree, or cause pruritus and consequent scratching and inflammatory phenomena. The *Pulex penetrans* or *sand-flea* is a minute brownish-red parasite which may penetrate the skin, and is found chiefly in tropical countries. The ovary of the parasite undergoes great distention in the skin, resulting in a painful edema and suppuration, which is occasionally accompanied by lymphangitis and gangrenous abscesses. The *Pulex irritans* or *common flea* produces merely a small hemorrhagic point as a result of the wound it inflicts. All other phenomena are inflammatory and dependent upon traumatism. *Craw-craw* is a rare affection occurring on the West Coast of Africa, chiefly among negroes, in which a parasite supposed to be related to the *Filaria medinensis* is responsible for a superficial but acute dermatitis.

Cysticerci have been found in tumors of the skin and subcutaneous tissue. These tumors project from the surface, are covered by unaltered integument, and are unproductive of subjective symptoms. They remain indolent for years. The *echinococcus* may be found in the skin. Among other parasites which may temporarily infest the human skin are the *Leptus autumnalis* or *harvest bug*, the *Acarus hordei*, the *ixodes* or *wood-tick*, the *Cimex lectularius* or *bedbug*, and several varieties of *culex* or mosquito, midges, etc. *Dipterous larvae* are occasionally found in or beneath the human skin. Of these, the most common is the *Æstrus bovis* or *gad-fly*. They usually produce suppurative inflammation.



FIG. 381.—*Leptus autumnalis* (after Küchenmeister).

ANGIONEUROSES.

INFLAMMATIONS.

Erythema Exudativum Multiforme.—Many writers regard erythema multiforme as a specific disease, but it results from so many diverse causes that this seems doubtful. It occurs in many infectious diseases, as typhus, syphilis, gonorrhea, etc., and is probably in some cases a metastatic bacterial dermatitis, different bacteria having been found by various observers in the blood and lesions. In other cases the lesions apparently are caused by an angioneurosis due to reflex action or to a toxin circulating in the blood. Osler,¹ who has carefully studied the visceral complications of erythema multiforme, defines it as a “disease of unknown etiology, with polymorphic skin lesions—hyperemia, edema, and hemorrhage—arthritis occasionally, and a variable number of visceral manifestations, of which the most important are gastro-intestinal crises, endocarditis, pericarditis, acute nephritis, and hemorrhage from the mucous surfaces.” The affection is closely related to rheumatism and purpura rheumatica. As further apparent causes of the disease may be mentioned anemia, chlorosis, debility, and the

¹ *Am. Jour. Med. Sci.*, Dec., 1895.

ingestion of drugs. The disease is most common in young adults and during the months of spring and fall, although it may occur at any age and at any season.

The morbid anatomy varies with the type of lesion, from congestion to milder grades of inflammation of the papillary and middle layers of the corium, or occasionally of the deeper layers and subcutaneous tissue. The persistent macules show some exudation of serum, with cells grouped about the vessels. In the papillary form of exanthem infiltration of the corium is greater and is not confined to the vicinity of the vessels. The lymph-spaces are dilated and the tissues more or less edematous. There may be proliferation and thickening of the rete, which also contains some wandering cells. In the vesicular and bullous types (*herpes iris*, *herpes circinatus*, *erythema bullosum*, *hydroa vésiculeux*, etc.) the exudate finds its way between the rete-cells, forming cavities either in the rete or between it and the upper layers. In all types the effusion is accompanied by an escape of red blood-cells, often in considerable numbers. A pigmentation may thus be left after the disappearance of the lesion.

In *erythema nodosum* the amount of the exudate is great, involving all of the cutis and usually portions of the subcutaneous tissue. There is marked dilatation of vessels and of lymph-spaces, with hemorrhages into the derma and subcutaneous tissues.

Erythema induratum is found chiefly on the legs of tuberculous young women, but is seen occasionally on other parts of the body or in individuals showing no trace of tuberculosis. The disease resembles clinically erythema nodosum, but the nodules break down and form typical "scrofulous" ulcers. The probable relation of this disorder to tuberculosis has not been determined.

Purpura (peliosis) rheumatica should be classed as an exudative erythema, in which hemorrhage, instead of being an occasional and unimportant feature, is constant and pronounced. The affection is associated regularly with rheumatic disorders. As in the exudative erythemas, the lesions are found chiefly in the papillary and deeper layers of the corium, where rupture of the walls of small vessels is frequently seen.

Pellagra.—In pellagra the skin lesions have, as far as is known, the histologic structure of other chronic exudative erythemas, and form but one feature of a constitutional disease. The skin participates in the general atrophy which follows repeated attacks. The immediate cause of the disease, which occurs usually among poor and uncleanly peasants as a result of eating decomposing grain, is probably a toxin which acts chiefly on the sympathetic and vagus. Postmortem examinations show characteristic pigmentary changes, together with hypertrophy, atrophy, and fatty degeneration of various organs. Sclerotic conditions of the brain and spinal cord and pachy-meningitis usually are found.

Acrodynia is probably closely related to pellagra. It is an acute disease, however, and anatomic changes have been demonstrated in but few cases. In these there were lesions of the cord and arachnoid.

Urticaria is an angioneurosis in which the idiosyncrasies of the individual play an important part, since many exciting causes are effective in certain individuals only, while in others commonly effective causes are wholly inert. The predisposition may exist as a part of many systemic disturbances, among which disorders of digestion and neuropathic conditions are the most

frequent, or it may be acquired by a skin irritated for some time by other diseases, such as eczema or prurigo. The exciting causes may be external, and include practically all forms of mechanical, thermal, or chemical irritation to which the skin can be subjected, but most frequently the chief cause is internal, as indigestion, mental or emotional disturbances, or an individual intolerance for certain foods, such as shell-fish, cheese, berries and other fruits, or for certain drugs. When any of the internal causes are present, slight external irritation of any sort will suffice to produce typical wheals.

Observers are not wholly in accord regarding the pathogenesis and anatomy of the disease. The most common belief is, that the wheal is formed by a brief spasmodic contraction of the vessels, followed by their paralytic dilatation and by retarded circulation. The ensuing exudation and edema produce the wheal, which is bright red at first, but soon becomes white in the center, owing to the rapidity with which the exudate extends in the tissues and forces the blood out of the vessels. Unna and others think the chief factor in the production of the wheal to be a spastic contraction of the muscular coats of the veins in the deep parts of the corium, with a resulting dilatation of the lymph-spaces, first in the deeper and later in the upper layers.

In *urticaria factitia*, besides the hyperemia and edema, which involve the rete to a slight extent, Unna describes a hyperplasia of the vessels, in which mast-cells play a conspicuous part, and an abundant epithelial mitosis. He thinks these changes may not be constant, but may be due to previously unnoticed irritation, and that the essential condition is some alteration as yet unrecognized in the nerves of the vessels. In a case of *urticaria factitia* of unusually severe reaction to stimuli, Gilchrist¹ found within fifteen minutes after the production of a wheal all the phenomena of acute inflammation of the entire corium. In speaking of this case, Welch suggested that in subjects of *urticaria* the blood contains toxins, some of which are set free into the tissues of the skin when the latter is irritated, producing true inflammations.

The hyperemia and edema of *urticaria* may be complicated by ecchymosis (*urticaria hemorrhagica*, *purpura urticans*), or the effusion of serum may be so great as to separate the layers of the epidermis and form blebs (*urticaria bullosa*). In persistent *urticaria* of children, especially of infants, the skin frequently becomes more or less covered with small inflammatory papules (*urticaria papulosa*, *lichen urticatus strophulus*), which are chiefly follicular, and are probably caused by local and reflex irritations of a sensitive skin.

In *urticaria pigmentosa* the papules and tubercles which persist after the subsidence of the wheals are made up of a more or less dense collection of mast-cells in the papillary body, with an accumulation of pigment in the basal layer of the rete. Unna² lays special stress on the constancy, number, and arrangement (in columns and largely about the vessels) of these cells. His recent observations, with those of Gilchrist³ and others, seem to disprove the opinion that the pigmentation of these papules is due to hemorrhage into the cutis. The persistency of the lesions and their manifest hyperplasia lead Unna to class the disease with the benign new growths.

Acute circumscribed edema (*angioneurotic edema*) has not been studied histologically, but is probably closely related to *urticaria*, except

¹ Johns Hopkins Hosp. Bull., July, 1896.

² Histopathology of Skin Diseases.

³ Johns Hopkins Hosp. Bull., July, 1896.

that it originates in the subcutaneous tissue, and is rarely, if ever, the result solely of external irritation. It is associated occasionally with urticaria, and can with difficulty be distinguished from the giant wheals found in *urticaria gigans*.

Prurigo.—The term “prurigo” is applied, unfortunately, by many writers to almost any chronic pruritic dermatitis if accompanied by the formation of more or less persistent papules. Though such lesions in their later stages may vary but slightly in their histopathology (the majority are due directly to traumatism), it is evident that primarily they may differ widely in their pathogenesis. The subject here considered is limited to the *prurigo of Hebra*, a disease beginning in infancy, and most common in Austria and some other European countries, where it occurs usually in the ill-nourished, unhygienic classes. Some observers believe the disease begins as an urticaria. Hebra and others describe a small subepidermic papule as the primary and essential lesion. Leloir states that this papule results from a cystic degeneration of cells in the rete, forming a cavity which at first contains a clear fluid, but later is filled with cellular débris, the walls of the cavity at the same time undergoing keratinization. It is possible that the papules result solely from traumatism of a pruritic skin, the pruritus arising from diverse causes. In an excellent presentation and summary of the subject, White¹ concludes as follows:

“I cannot go further than accept the existence of a condition of early childhood, allied to pruritus and urticaria in its visible manifestations, and not to be positively distinguished from them in its first stages, often becoming in certain parts of the world a chronic affection due to some inexplicable national cutaneous traits, or inherent customs of living, a condition which certainly lacks many of the essential elements of individuality.”

DERMATITIS OF NEUROTIC, TOXIC, AND OBSCURE ETIOLOGY.

Dermatitis may be acute or chronic, and may vary in degree from the border-line of simple congestion to the several forms terminating in necrosis and gangrene. The process may be limited to the upper or lower layers of the corium or may extend to the subcutaneous tissue beneath. When the upper layers are affected the papillæ may be edematous and enlarged, producing papules; the epithelial cells may be separated by the effusion or undergo colliquative necrosis, resulting in the formation of vesicles, bullæ, and pustules. An attempt to classify these forms of dermatitis according to their histologic structure is futile, since the pathologic process depends not only on the nature—mechanical, chemical, thermal—of the cause, but also upon the intensity and duration of its action and upon the previous condition of the tissues involved.

The great majority of inflammations—and especially the chronic forms—of the skin are considered with the many diseases of which they form a part, but it is convenient to consider separately a few independent types of dermatitis. **Traumatic dermatitis** is due to mechanical (often combined with chemical or thermal) irritation, such as contusions, abrasions, lacerations, etc. Under this head should be included *dermatitis artificialis* and

¹ Discussion by Bésnier, Kaposi, White, Payne, Neisser, Touton, Petri, and Feulard, *Trans. Third Internat. Cong. of Derm.*, London, 1896.

feigned skin diseases; dermatitis calorica due to extreme heat—*dermatitis ambustionis*—or to extreme cold—*dermatitis congelationis, chilblain, pernio*.

Dermatitis venenata is produced by a chemical irritation of the skin, and may result from contact with any one of a vast number of vegetable, animal, and mineral products. The most common are poison ivy and other plants; and drugs, chemicals, dyes, etc. used in surgical dressings, in the arts and trades, and for domestic purposes. Individual idiosyncrasy is an important factor in the majority of cases. Absorption through the skin may occur, and produce a mild systemic toxemia, frequently with the production of new areas of dermatitis at some distance from the original.

Dermatitis medicamentosa includes all forms of congestion and of inflammation of the skin due to the introduction into the system, through the alimentary tract or through the skin, of medicinal agents. Etiologically and pathologically the condition may be classed with the symptomatic and multifiform erythemas. The immediate irritating agent may be the drug itself or some toxin produced during its absorption and elimination. When due to local application of a medicament, the process is that of a *dermatitis venenata*.

The type of eruption produced by any one drug is not constant, although the acneform lesions due to bromin and iodin, and the erythemas due to belladonna, quinin, antipyrin, and a few other drugs, are often characteristic. The compounds of iodin, bromin, and arsenic may cause severe types of dermatitis, occasionally leading to the production of ulcers, fungous growths, and even death.

Gangrene of the skin may follow severe grades of any acute dermatitis. There are a few distinct types, however, of gangrene of the skin which deserve special mention. *Dermatitis gangrenosa infantum* is a rare disorder which is seen in debilitated children usually under three years of age. The lesions are due undoubtedly to the infection of tissues possessing feeble powers of resistance to micro-organisms. Various forms of diplococci, staphylococci, and streptococci have been demonstrated in the lesions. The condition has been reported as following varicella and vaccinia, but no definite relation to these diseases has been established. The lesions appear upon erythematous spots as vesicles and pustules, which soon form crusts, under which gangrenous ulcers develop and spread. These ulcers may be small, superficial, scattered, and few in number; or they may be deep enough to involve the subcutaneous tissue, and so numerous as to cover large areas.

Spontaneous gangrene and *multiple gangrene* in adults occur after local infections, but are seen most frequently in young hysteric women, and, as a rule, are factitious.

Diabetic gangrene occurs as a result of the slightest injuries to the skin, or even spontaneously, in individuals suffering from diabetes mellitus. The etiology of the affection is obscure. Probably local infection of weakened tissues and neurotic changes are responsible for the condition. The vascular changes have not been thoroughly studied.

Eczema is inflammation of the skin characterized by multiform lesions, pruritus, an irregular course, and a tendency to persist or recur. It may be acute, but is usually chronic. Although, as the most common of skin diseases, it has been the subject of careful study by many competent observers, its causes and pathogenesis are yet undetermined.

Any systemic or local condition that interferes with the normal nutrition

and function of the skin modifies and prolongs the course of eczema or acts as a predisposing cause. The disease is frequently seen in systemic disorders due to defective elimination, and metabolism, such as rheumatism, gout, etc.; in various toxemias; and in simple malnutrition. It is sometimes due to neurotic conditions or to reflex disturbances.

In some cases the location of the lesions seems to be determined by nerve distribution—*neuritic eczema*. In individuals predisposed to eczema the exciting external causes may be any of those mentioned for dermatitis. Some forms of eczema (besides eczema seborrhoicum and eczema marginatum) are undoubtedly due to, and many others influenced by, the local action of parasites.

The histologic changes in eczema are those of inflammation in the corium and consequent changes in the epithelium. In acute eczema there are dilatation and congestion of the blood-vessels, with an abundant effusion of serum and escape of leukocytes into the connective tissue, the fibers of which are swollen and compressed. There are also proliferation of the connective-tissue corpuscles and dilatation of the lymph-spaces. The process may be moderate and limited to the papillae and upper layers of the corium; or it may extend even to the subcutaneous tissue and produce an extensive edema and swelling suggestive of erysipelas. When superficial the changes may be diffuse or circumscribed, as in the papular form, which Robinson states always begins about the follicles. In the rete there are both cellular and intercellular edema and a varying number of migrating cells. Vesicles and even bullae may form between the rete and the granular or horny layer from separation of the cells by the exudate; or vesicles may appear in the rete as a result of a colliquative degeneration or "cavernous transformation" (Unna) of a number of cells and the merging together of the small cavities thus formed. The vesicles contain serum, some fibrin, free nuclei, and a few leukocytes, which increase in number if the vesicle is transformed into a pustule. Robinson states that the exudate in eczema acquires its peculiar sticky, gummy character from the destroyed epithelial cells. There are hyperplasia of the rete, and in the upper layers anomalous cornification and exfoliation. In *eczema rubrum* the entire process is more intense and deeper; the entire horny layer is thrown off, exposing the rete, which may be partially destroyed, or be covered with exudate and with degenerated or imperfectly cornified cells. In *squamous eczema* there are marked parakeratosis and desquamation, with but moderate changes in the rete and corium.

In *chronic eczemas* the secondary inflammatory changes (proliferation and hypertrophy of connective tissue and deposit of pigment) in the corium and the hyperplasia of the rete become more and more marked, producing great thickening of the tissues, with occasional verrucous and papillomatous growths. Infiltration and hypertrophy may extend to the subcutaneous tissue, destroy the fat-cushion, attach the deeper tissue firmly to the cutis, cause atrophy of the glands and hair-follicles, and, by obstructing veins and lymphatics, produce an elephantiasic condition.

Unna teaches that an acute vesicle of eczema is due to an infection by the "morococcus," followed by a spiral form of chemotaxis, and that all other forms are due to parakeratosis, acanthosis, and a "spongy transformation of the prickle layer."

Eczema folliculorum (Morris) has been examined histologically by Jadassohn, who states that the condition is a nonsuppurative folliculitis

with no changes in the interfollicular tissue, and therefore is not a true eczema. It is probably parasitic in origin.

Eczema marginatum and *seborrheic eczema* are considered under separate heads.

Eczematization and *lichenification* are terms first given by French writers to persistent local lesions (usually papular or squamous) of the skin due to continued traumatism and scratching, while *neurodermatitis* is applied to such lesions when their first appearance is preceded for some time by localized pruritus, or when they occur without external cause. Considerable confusion still exists among writers regarding the exact use of these terms, which have been introduced for the sake of etiologic distinctions, the histology of the lesions being that of chronic dermatitis or chronic eczema.¹

Seborrheic eczema (*eczema seborrhoicum*) is now generally accepted as a definite disease, though few dermatologists are willing to include under this head all the phenomena that Unna claims for it. In his original description of the affection, Unna claimed for it a parasitic origin, and found in the lesions three varieties of diplococci, one of which was his *morococcus* of eczema and Malassez's flask-shaped bacillus. Elliott's² observations and Merrill's³ bacteriologic investigations need only confirmation to demonstrate the parasitic origin of the disease. Other investigators report the finding of various micro-organisms in the scales, but the final proof is wanting. Locally, heat, moisture, and friction favor the origin and development of the disease. A constant covering on the head favors its occurrence on the scalp. The predisposing causes named in connection with eczema and seborrhea should be considered.

Histologically, according to Elliott and Unna, in the mildest forms, usually known as *pityriasis capitis*, there are found in the derma evidences of superficial inflammation; in the rete, vacuole-like formations in the basal layer, some mitoses, and a few wandering cells; and in the horny layers parakeratosis and desquamation. In the severer grades, marked by redness, moisture, and crusting, the changes in the corium are deeper and more pronounced, a decided edema being present at times; in the rete there is marked increase in the number of mitoses and of wandering cells, together with more or less nuclear degeneration and cell destruction. In all forms the horny layer is thickened, imperfectly cornified, and easily detached except about the dilated follicular openings, which are packed with horny cells. The granular layer is usually thickened. The sebaceous glands are unaffected, but the coil-glands are often dilated, show mitoses and cell degeneration, and contain cast-off epithelial cells and granular debris. Unna found fat in the coil-glands, which he believes to be the source of the fat in the characteristic secretion, and in the lymph-spaces of the cutis and epidermis. Elliott found no evidences of fat in the coil-glands or in the lymph-spaces.

Dermatitis repens is a name given by Crocker to a rare form of spreading dermatitis starting from an injury to the skin. There is a free exudate, forming vesicles and bullæ, with resulting complete denudation of the rete. The process spreads slowly by direct extension as the older portions heal. It is undoubtedly parasitic in origin, as it persists indefinitely unless checked by antiseptic treatment. Its histopathology has not been studied.

¹ For a good review of the subject, see Török, *Ann. de Derm. et de Syph.*, Dec., 1896, and Touton, *Arch. f. Derm. u. Syph.*, Nov., 1895.

² *Morrow's System*, vol. iii. ³ *N. Y. Med. Jour.*, Oct., 1895, and Mar. 4, 1897.

Herpes zoster (*zoster* ; *zona* ; *shingles*) is believed generally to be a neurosis due to pathologic changes in some portion of the nervous system. The lesion reported most frequently is an inflammation of the posterior ganglion and trunk of the nerve supplying the portion of skin on which the vesicles are seated. Various conditions of different parts of the central nervous system have been described as productive of zoster, while in some cases a peripheral neuritis alone could be found. Just how these morbid changes in various parts of the nervous system produce the lesions on the skin is not understood. Pfeiffer and Wasielewski have endeavored to show that zoster is a herpetic inflammation due to blocking of the fine capillaries with micro-organisms. Ebstein¹ believes in its angioneurotic origin. Other observers consider the disease bacterial in origin. Zoster has been attributed to many and varied causes, including all manner of injuries to nerves and nerve-centers, exposure to cold and especially to cold draughts, the internal administration of arsenic, climatic influences and especially the changes common in spring and fall, tuberculosis, malaria (Winfield), and other organic and functional disorders. It occurs occasionally in small epidemics. With but few exceptions, zoster affects an individual but once, and that usually before the twenty-fifth year. The histologic changes in the skin begin in the rete-cells, which undergo rapid proliferation, some of them increasing greatly in size. Cavities are formed containing portions of degenerated cells. Protozoa-like bodies are described by Hartzell and others. Inflammation of the papillary body follows, and the cavities in the rete coalesce to form vesicles, which have for a roof the horny layer, and for a base the papillary body or the deepest layer of rete-cells. Gilchrist² describes in the macule which precedes the formation of the vesicle a remarkable multiplication and accumulation of nuclei in the rete without an increase in karyokinetic figures, a result of direct budding of nuclei and fragmentation of surrounding parts (Welch).

Herpes simplex (*herpes facialis* ; *herpes labialis* ; *herpes progeneritalis*) appears from a variety of causes in individuals predisposed to the affection. Recurrences are the rule. The exact genesis of the condition is not understood, but it is due probably to a local or reflex neurotic disturbance. A microbic origin is possible, but not demonstrated. Herpes facialis frequently accompanies febrile disorders, indigestion, and other systemic disturbances. Herpes progeneritalis may be due to various reflex influences or to local irritation of various forms to which the genitals are subjected during menstruation, copulation, the course of venereal disease, or to the persistence of the effects of such disease on the local tissues. Retained secretions and lack of cleanliness may furnish the necessary irritation.

Dermatitis herpetiformis (*Duhring's disease* ; *hydraea herpetiforme* ; *dermatitis multiformis* ; *herpes gestationis* ; *pemphigus pruriginosus*, etc.) is now generally accorded recognition as a disease *sui generis*. Its etiology and pathogenesis are not definitely determined, though it is undoubtedly neurotic in origin, due to vasomotor or other reflex disturbances. Seemingly, it is closely related to urticaria, zoster, erythema multiforme, and pemphigus. Duhring³ himself would give the disease a position between the two last-named affections, from which in typical cases it is distinguished with difficulty. Among the varied causes assigned are pregnancy, renal and

¹ *Virchow's Archiv*, Bd. cxxxiv., H. 3.

² *Johns Hopkins Hosp. Rep.*, vol. i.

³ *Am. Jour. Med. Sci.*, p. 169, Feb., 1897.

other organic diseases, general debility, nervous exhaustion, and other physical, mental, and moral conditions that may injure the nervous system.

The lesions have recently been studied in detail by a number of observers, including Leredde and Perrin,¹ Gilchrist,² Darier,³ and others. In

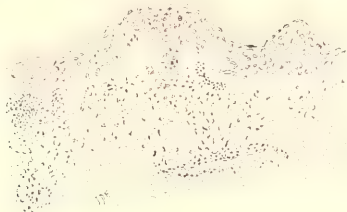


FIG. 382.—Dermatitis herpetiformis: section through two minute vesicles, showing infiltration and edema of the corium, the vesicles lying entirely beneath the epidermis.

brief, the process is an acute inflammation of the papillary body, the deeper layers of the derma being unaffected, while the epidermis plays a passive part only. Edema is present in every case, and is often excessive. The number of polynuclear, small mononuclear, and red blood-cells that escape



FIG. 383.—Shows part of the larger vesicle in Fig. 382, under $\frac{1}{2}$ oil immersion: eosinophiles are very numerous, three of them having wandered up between the rete-cells; the vesicle contains much fibrin, with lymphocytes and polymorphonuclear leukocytes.

into the tissues and into the vesicles between the derma and the rete is remarkably large, though in the deeper portions of the affected areas the cells are

¹ *Ann. de Derm. et de Syph.*, 1895 and 1896. ² *Johns Hopkins Hosp. Rep.*, vol. i.

³ *Ann. de Derm. et de Syph.*, p. 542, 1896.

found chiefly about the vessels. The fibrinous character of the exudate is manifest. Large numbers of eosinophiles are found in the blood, in the vesicles and tissue immediately beneath them, and even between the rete-cells. There is apparently an elimination through the skin of the excess of eosinophiles in the blood. The importance of these cells is doubtful, since they have been found in vesicles produced artificially. When pustules occur they are due probably to secondary infection.

Impetigo herpetiformis is a rare pustular, usually fatal disease, found, with but two or three exceptions, in pregnant women. Formerly, Dühring considered it a form of dermatitis herpetiformis, but it is probably a distinct affection. About 20 cases have been reported, so that the pathology of the disease is not understood. The pustules are superficial. Post-mortem findings point to its being a septic process, a "metastatic pustulosis" (Neumann), though some observers believe it to be a neurosis.

Pemphigus, in common with other bullous dermatoses, is at present the subject of much active investigation. Many conflicting opinions exist regarding the nature and relations of its several varieties. The majority of writers, however, consider under this head *pemphigus vulgaris*, *acute* and *chronic*; *pemphigus foliaceus*; and *pemphigus vegetans*.

Pemphigus acutus contagiosus neonatorum, and a similar contagious bullous eruption of tropical countries, described by Manson, are probably distinct diseases of microbic origin. Unna excludes also *pemphigus vegetans*, which he describes, under the name *erythema bullosum vegetans*, as a "local infectious, auto-inoculable dermatosis."

Pemphigus is closely related pathogenically to dermatitis herpetiformis and to zoster. In the majority of cases it is associated directly or indirectly with organic or functional disease of brain, cord, or nerves, and is considered by many a trophoneurosis. In other cases, however, post-mortem examination has failed to discover any lesion of the nervous system, and the disease may occur in persons in whom no other disorder can be detected. Chills (Crocker), hysteria (Dumesnil), traumatisms, and many other causes for the disease are given. Whipple¹ has recently found in bullæ of pemphigus a diplococcus corresponding accurately to that previously described by Demmé, Claessen, and Bullock, and has carried out a series of culture and inoculation experiments that have furnished strong presumptive evidence of the microbic origin of the disease. Pernet and Bullock² describe a series of fatal cases, occurring in butchers, due to local infection of a wound. An increase in the number of eosinophiles in the blood and in the bullæ has been demonstrated in some cases, but is neither so constant nor so pronounced as in dermatitis herpetiformis.

The histopathology of pemphigus is variously described by different observers. Many consider the process a primary inflammation of the skin, but Auspitz and others believe all phenomena of inflammation are secondary to a sudden escape of fluid from the vessels of the derma, producing pronounced edema of the papillæ, mechanically separating and stretching the rete-cells until the spaces between them unite to form bullæ. The bullæ contain serum chiefly, and are usually described as being superficial, having the outer layers of the horny cells for a roof and the rete for a base. According to Crocker and others, the bullæ may be deeper and form entirely within the rete. Later the upper parts of the derma may present

¹ *London Lancet*, May 2, 1896.

² *Brit. Jour. of Derm.*, pp. 157 and 205, 1896.

evidences of inflammation. Slight hemorrhage may occur in the bullæ (*pemphigus hæmorrhagicus*, *purpura bullosa*); the base of the bullæ may be covered with coagulated lymph (*pemphigus diphtheriticus*), or in rare instances may be necrotic (*pemphigus gangrænosus*). Unna believes that *pemphigus vegetans* begins with paralysis of the blood-vessels and stasis, followed by swelling of the upper layers of the cutis, elevation of the horny layer, and epithelial necrosis. In the crusting stages he describes a marked dilatation and turgescence of the capillaries immediately under the crusts, with small hemorrhages from the capillary loops. The deeper vessels are less affected, and the cutis as a whole is little altered. The stasis leads to epithelial necrosis, which extends to the connective tissue of the corium. Later the rete-cells produce irregular and grotesque-shaped growths and thickenings under the necrotic areas, and cause irregular elongations and growths of the papillæ. He describes also remarkable alterations in the coil-glands.

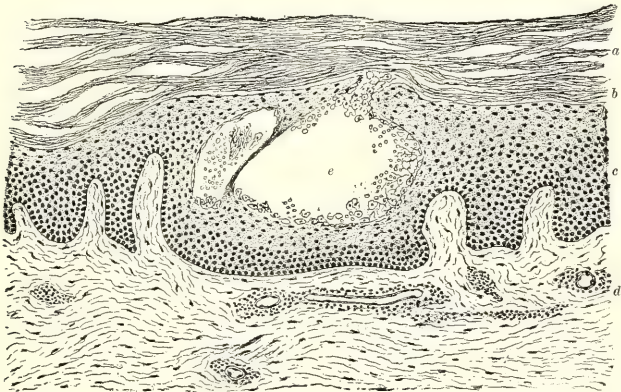


FIG. 384.—Vesicle in pompholyx: *a*, corneous layer *b*, stratum lucidum; *c*, rete; *d*, corium; *e*, vesicle. The sweat-glands are normal and show no connection with the lesions (Robinson).

Pompholyx (*cheiropompholyx*; *dysidrosis*) is characterized by the formation of deep-seated vesicles on the palms and soles. It is probably a neurosis and closely allied to pemphigus. A nervous temperament, worry, fatigue, and nervous depression from any cause seem to be factors in producing the disease. Though Tilbury Fox believed the vesicles were due to occlusion of the sweat-ducts, and Crocker states that a minority of the vesicles may be so formed, the researches of Robinson,¹ Unna, and Williams,² point clearly to the inflammatory nature of the vesicles and their independence of the sweat-glands, which are histologically unaltered, although hyperidrosis usually precedes pompholyx. The vesicles begin in the upper part of the rete, the cells of which become flattened and drawn out, by the pressure of the liquid, into fibers separating small loculi, which eventually unite, by rupture of the fibers, to form part of the vesicle. The

¹ *Arch. of Derm.*, p. 289, 1877; also *Morrow's System*, vol. iii., p. 184.

² *Monat. f. Derm.*, p. 41, 1891.

vesicles contain serum, fibrin, and albumin, and in the later stages pus-corporuscles. The upper layers of the corium are involved in a mild inflammation, but the deeper tissues are not involved. Robinson describes small sweat-filled cavities in the horny layer. Unna describes minute changes in the horny cells over the center of each vesicle, and a bacillus which he thinks is the cause of the disease.

Epidermolysis bullosa hereditaria (*acantholysis bullosa*) is a rare condition, usually hereditary and first manifested in infancy, in which bullæ rapidly form on any part of the skin that is slightly rubbed or bruised. The bullæ are situated in the lower part of the rete, resting partially on the papillæ. There is pronounced edema of the upper part of the corium and of many of the rete-cells, but the horny layer is not involved. In a recently formed bulla Elliott¹ found evidences of inflammation about the deeper vessels of the corium. In the apparently normal skin of these individuals he has demonstrated a peculiar granular condition of the deepest layer of rete-cells.² The disease is a traumatic dermatitis in individuals whose skin responds excessively to the slightest external irritation.

Hydroa vacciniforme is a rare disorder, usually beginning in infancy and occurring in persons of a peculiar predisposition, in which exposure of the skin to the sun's rays, or in some instances to artificial heat or to cold winds, is followed by the production of characteristic vesicles on the surface so exposed. The pathogenesis of the disorder is not understood. The histology of the lesions has been studied by Bowen,³ Brocq, and Mibelli.⁴ The process apparently begins as an inflammation of the upper part of the corium, with vesicle formation in the middle layers of the rete. This is followed by a sharply circumscribed necrosis involving the lower horny cells, the rete, and the corium nearly to the subcutaneous tissue. This necrosis is the cause of the central dark depression of the varioliform vesicle, and of the resulting scar, which closely resembles the scar of variola and of necrotic acne. Under the names *hydroa æstivale*, *hydroa puerorum*, and *summer prurigo* are described cases which resemble hydroa vacciniforme, but in these conditions the lesions are pruritic and more superficial, while necrosis and scarring are absent or slight.

Lichen planus (*lichen ruber planus*) is now acknowledged by most writers to be a distinct and separate affection from lichen ruber. The causes of lichen planus are obscure, and frequently none can be determined, though the disease is seen most frequently in persons of neurotic temperament or as a result of some disturbance of the nervous system. Observers are not wholly in accord regarding the histologic changes. According to Crocker's description,⁵ which agrees in the main with that of Török,⁶ the process is an inflammation of the upper layers of the corium with secondary changes in the epidermis. The papillæ and a narrow, sharply outlined zone of tissue beneath them are infiltrated with cells like leukocytes, and are more or less edematous. The rete-cells undergo proliferation, which in chronic cases may be so excessive as to obliterate the papillæ, or, on the contrary, to enlarge them by downgrowth of the interpapillary processes. In acute cases the hyperplasia of the rete-cells is not so evident, the rete

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, Jan., 1895.

² *Ibid.*, Nov., 1899.

³ *Ibid.*, March, 1894.

⁴ *Monat. f. prakt. Derm.*, Bd. xxiv., S. 871.

⁵ *Diseases of the Skin*, 2d ed., 1893.

⁶ *Jour. des Mal. cutan.*, 1889.

being crowded upward, and even thinned in the center, by the cell infiltration. The horny layer is slightly thickened, and in the later stage forms a conical mass at the mouth of the sweat-duct. The exfoliation of this plug forms the central depression of the papule. Török believes the center is held down by the sweat-duct. The hairs and glands are not involved. Unna states that the cells collected in the center are connective-tissue cells, and that "characteristic epithelial changes coexist: in an initial acanthosis (hyperplasia) which later gives place to epithelial atrophy, in a persistent hyperkeratosis which leads to the formation of varied horny structures, in a permanent intercellular edema, and a widespread colloid degeneration of the prickly layer." He describes hyaline degeneration and sclerotic changes in the connective tissue, and cyst formations of the coil-glands, and gives in detail the histologic structure of seven different forms of lichen planus

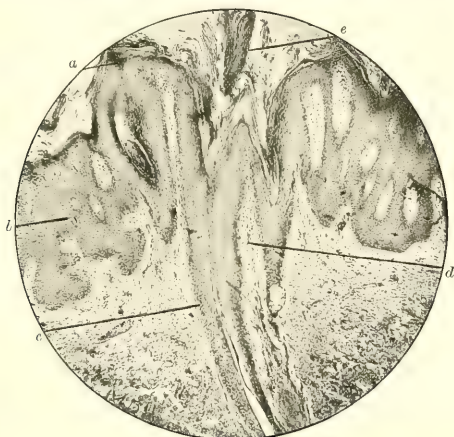


FIG. 385.—Section from a patch of pityriasis rubra pilaris: *a*, thickened corneous layer; *b*, hypertrophied rete; *c*, hair-follicle; *d*, cell infiltration about follicle; *e*, corneous plug in mouth of follicle (Hartzell).

papules and patches. Joseph¹ has recently described a vesicle formation between the rete and papillæ, and believes the umbilication of the papule is due to absorption of the vesicular contents.

The *hypertrophic* and *verrucous* forms of lichen planus have been studied recently by Fordyce and by Joseph. Fordyce² describes in the cutis marked evidences of chronic inflammation, including connective-tissue hypertrophy. He states that the changes extend even into the subcutaneous tissue, and that there are excessive hypertrophy of the horny, granular, and mucous layers, downgrowths of the interpapillary processes, moderate leukocytic infiltration, and colloid degeneration in the epidermis.

Lichen ruber acuminatus (of Kaposi) is now generally conceded to be identical with the *pityriasis rubra pilaris* of French authors (Devergie,

¹ *Arch. f. Derm. u. Syph.*, Jan., 1897.

² *Jour. Cutan. and Gen.-Urin. Dis.*, Feb., 1897.

Besnier, and others), and is probably the same condition first described by Hebra as *lichen ruber*. The nature of the disease is not understood. Histologically there is found an exaggerated keratinization of the epithelial wall of the mouth of the pilosebaceous follicle, thickening of the rete with irregular hypertrophies of the interpapillary processes, thickening of the horny layer with imperfect keratinization of the cells, and evidences of a secondary inflammation in the corium (Fig. 385).

Dermatitis exfoliativa (*pityriasis rubra* of many writers) is a term somewhat loosely applied to a universal or generalized condition of the skin, characterized by inflammation and by exfoliation of the epidermis. It may occur apparently as an idiopathic disease, but is described often as consecutive to eczema, psoriasis, lichen ruber, and other forms of dermatitis. As an independent affection it may be subacute and probably identical with the more persistent forms of *scarlatiniform erythema*, or chronic and indistinguishable from the later exfoliating stages of psoriasis, eczema, etc. In a number of cases which he had kept under observation during the gradual development of exfoliative dermatitis from psoriasis and from pityriasis rubra pilaris, Besnier found the histologic changes to be independent of the origin of the disorder. In acute or recent idiopathic cases, Crocker and others describe a superficial inflammation of the corium with the usual vascular dilatation, edema, and cell infiltration; an increase in size of the interpapillary processes, but a thinning of the rete as a whole; and separation of the upper two-thirds of the horny layer. In the later stages the inflammation is deeper, and may be accompanied by some connective-tissue formation and by proliferation of rete-cells. In cases of long standing there is usually a thickened horny layer, with more or less atrophy of the rete and of the corium, including hair-follicles and sebaceous glands. The stratum granulosum and stratum lucidum are usually obliterated.

The rare, usually fatal *pityriasis rubra* described by Hebra is thought by some to be but a severe form of exfoliative dermatitis; by others it is considered a distinct affection. There are certainly good clinical grounds for making a distinction between the two conditions, though transitional types are described. The histologic changes in pityriasis rubra apparently correspond with those in the chronic cases of exfoliative dermatitis. As further changes there are reported sclerosis of the connective-tissue fibers of the derma, and the deposition of pigment-granules in the remaining portion of the rete. In a number of cases Jadassohn found the condition associated with tuberculosis of other organs.

An *exfoliative dermatitis* has been described by Ritter as occurring in infants from one to five weeks old. The symptoms vary from an exaggeration of the physiologic exfoliation (Kaposi) to those of pemphigus foliaceus (Behrend). Its pathology is not understood. Ritter thinks it septic in origin. Cases have been reported in America by Elliott, Morton, and White.

An *epidemic exfoliative dermatitis* has been described by Savill and others. In it a diplococcus, differing slightly in cultures from the *Staphylococcus albus*, was isolated. Echeverria¹ made histologic examinations of 2 cases, and describes a superficial inflammation with epidermal changes, including a strange kind of degeneration of the nuclei of the rete-cells.

Pityriasis rosea (*pityriasis maculata et circinata*; *herpes tonsurans*

¹ Brit. Jour. of Derm., Jan., 1895.

maculosus) is an acute self-limited, superficial inflammation of the skin, accompanied by furfuraceous desquamation. It is seen most frequently in delicate young adults, but also in healthy individuals. The eruption may be preceded or accompanied by slight febrile disturbance, and is probably due to a systemic infection, and not to the local action of a parasite, as believed by Kaposi. In the bacteriologic investigation of the disease by Oro and Mosea,¹ examinations of the blood and tissues were negative, though pus cocci and a bacillus were demonstrated in the scales and cultivated. Unna showed a superficial inflammation with decided edema and cell infiltration of the cutis and the lower part of the rete; acanthosis and parakeratosis of the epithelium; parenchymatous edema of the upper rete-cells; and minute irregular "subcorneal pressure vesicles," not visible macroscopically.

Pityriasis circiné et marginé of Vidal is probably a form of *seborrheic dermatitis* or of *eczema marginatum*.

Psoriasis is usually a chronic affection, but may be acute. Little is definitely known of its pathogenesis. It occurs in both sexes and at all ages, though it is rare in infants under two years, and does not commonly begin after fifty. Some cases seem to depend upon an inherited predisposition, or upon a rheumatic, gouty, or other diathesis. It is a common affection, and its occurrence with other diseases, sometimes named as causes, is easily explained on the ground of coincidence. In a person subject to the disease an external irritation, such as a scratch, may determine the location of new lesions. Cases are reported that were apparently due to contagion. Different micro-organisms in the scales have been described, and one or two apparently successful inoculations have been reported.

The histology of the lesions has been studied by Robinson, Crocker, Reis,² Schutz,³ Piffard,⁴ Unna, and others. Older writers describe an inflammation of the corium as the primary process; but the majority of later observers think this inflammation is secondary to changes in the rete or in the transitional layers of the epithelium. Some believe the process begins as an anomaly of cornification, which is followed by hyperplasia of the rete and inflammation in the corium; others think the first step is hyperplasia of the rete. The horny layer is thickened greatly as a whole, but the cells are more or less separated from each other, forming spaces in which are seen nuclear fragments which may be epithelial or derived from leukocytes. In the spaces are found also bodies supposed by some to be micrococci, together with air, which gives to the scales their silvery appearance. The cells are imperfectly cornified, and in the lower third or more retain their nuclei and staining properties. Keratohyalin and eleidin have quite, or nearly, disappeared from this layer and from the stratum lucidum. The stratum granulosum is usually thickened, but in places may be thinned or absent. In the rete the cells undergo proliferation, there being often two, three, or four rows of palisade-cells. The interpapillary processes enlarge vertically and horizontally and penetrate quite deeply into the corium, but immediately over the papillæ the rete is usually thinner than normal. The changes in the corium are those of moderate inflammation, with effusion of serum and cells into the deformed and enlarged papillæ and about the vessels

¹ *Sulla Pityriasis Rosea*, Sienna, 1894, includes a review of literature to date.

² *Viertelj. f. Derm. u. Syph.*, 1888.

³ *Arch. f. Derm. u. Syph.*, 1892.

⁴ *Jour. Cutan. and Gen.-Urin. Dis.*, 1893.

of the corium. Unna thinks the increase in cells is chiefly from connective-tissue elements. These changes may extend down about the follicles and sweat-ducts. The sebaceous glands are not affected.

Lupus erythematosus is believed by Besnier and his followers to be a form of tuberculosis, because of its frequent occurrence in individuals suffering from general forms of the disease. But lupus erythematosus occurs with equal or greater frequency in individuals showing no trace of tuberculosis, and histologic and bacteriologic researches have failed to establish any relation between the two diseases. Lupus erythematosus appears usually in the third decade of life, and much more frequently in women than in men. It usually appears independently of other diseases, but may follow seborrhea, acne, traumatism, acute or chronic dermatitis, erysipelas, pernio, or other circulatory disturbances. By some writers it is considered a chronic inflammation due to a specific infection.

The histopathology of the disease has been studied by a number of observers, who differ considerably in their reports and conclusions. The changes are chiefly those of a chronic inflammation in the upper parts of the corium. The infiltration of small round cells, some leukocytes, and proliferating connective-tissue cells varies greatly in extent and in density in different types of lesions, but is most marked about the vessels, the follicles, and the glands. Granular, fatty, or colloid changes affect isolated cells, which disappear, and are replaced by others. Similar changes occur in the connective-tissue fibers. There are no nodules, no giant cells, and no destruction of cells en masse, as in lupus vulgaris. The blood-vessels are often distended with red blood-corpuscles, and may show obliterating endarteritis. Localized or diffuse hemorrhages may occur. The sebaceous glands early in the disease are stimulated to hypersecretion, and may enlarge. Later they and the coil-glands become involved in the cell infiltration and the succeeding retrograde changes and disappear, producing frequently a small atrophic punctate scar. The epidermis is thinned and atrophied. The interpapillary processes and papillæ largely disappear. Capillary thrombosis and embolism have recently been demonstrated in the lesions by Fordyce and Holder,¹ who believe the disease begins with a disturbance in the local circulation.

TUMORS.

Molluscum contagiosum (*molluscum epitheliale*; *molluscum verrucosum*; *epithelioma contagiosum*) occurs most frequently in children whose habits and surroundings are unhygienic, though it is found also in adults and independently of hygienic deficiencies. It may appear in small epidemics (Stelwagon²), and is undoubtedly contagious, though but few inoculation experiments have been successful.

The lesion in molluscum contagiosum is made up of a number of conical bodies, separated from each other by fibrous septa, converging at their apices to a common central opening. The growth is entirely in the rete, the papillæ being obliterated, or compressed and elongated to form septa between the lobules. The lower or outer cells of each lobule are usually normal and correspond to the palisade-cells of the rete, with which, at the border of the

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, May, 1897.

² *Ibid.*, Feb., 1895.

growth, they are continuous. Above them are cuboidal epithelial cells, which undergo gradual degeneration toward the center of the growth, where they form a soft, homogeneous, yellowish mass, which can be pressed out of the central opening. The more minute changes, as well as their nature and significance, are matters of dispute. By some the cell is said to undergo a homogeneous amyloid degeneration, the substance thus formed gradually filling up the entire cell, enlarging it, obliterating its structure, and forming the so-called molluscum-body. The majority of observers describe the formation of clear oval spaces or bodies in the cell, beginning in the neighborhood of the cell-nucleus. These oval bodies are themselves seemingly provided with a nucleus, and gradually expand to fill the whole interior of the cell. In its later stages the body is seen as a finely granular mass surrounded by a clear, transparent zone. Still later the exterior of the cell may undergo excessive cornification, a feature which constitutes the chief

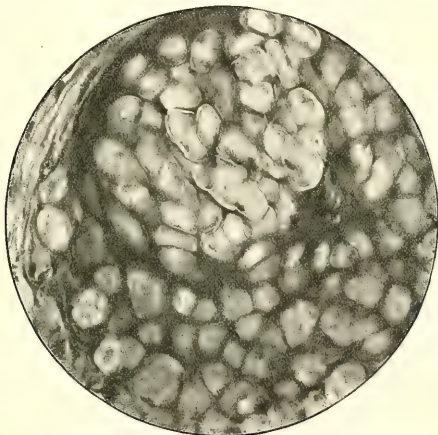


FIG. 386.—Molluscum contagiosum, showing group of typical molluscum-cells (S. Pollitzer's case, section, and photomicrograph).

change in some cells. By a few observers these cell-forms found in molluscum are still believed to be protozoa, but the majority think with Gilchrist and Kuznitski,¹ that these figures are produced by changes in the epithelial cells. These changes begin probably as in true epithelioma, in the deeper rete-cells, though the process may start in the mouth of the follicles. Beck believes the primary change is found in the pigment-cells of the rete. The growth is not, as was formerly supposed, connected with the sebaceous glands.

Keloid is commonly divided into *true* or *spontaneous*, and *false* or *cicatricial*, keloid. It is probable, however, that all keloid is cicatricial in origin, though the preceding lesion of the skin may not be recognized. In persons predisposed to keloid the growth may follow slight traumatism, or even vesicles, pustules, or other insignificant lesions, which of themselves

¹ *Arch. f. Derm. u. Syph.*, Bd. xxxii., 1, 2.

do not produce scars. This tendency to keloid formation is most common in negroes. The cause of keloid is not known, though by many it is supposed to be microbic. Hyde suggests that some cases are probably forms of tuberculosis of the skin. Histologically the growth consists of dense bundles of connective tissue, the fibers of which usually run parallel to the long axis of the tumor and to the surface of the skin, though some vertical and oblique fibers are usually present. In the center and older parts of the growth there are comparatively few vessels, about which are scattered nuclei and spindle-cells. Toward the border the number of vessels and cells increases gradually. A cell-growth is found in the adventitia of the vessels for some distance beyond the limit of the tumor, and it is probable that keloid develops from these cells, which undergo changes to spindle-cells, and later to fibers. The new-formed fibers include the tissue of the corium in the new growth. The attempt to distinguish spontaneous keloid from cicatricial keloid by the presence in the former and absence in the latter of papillæ and rete-cones does not succeed. The papillæ and interpapillary processes may be well or but slightly developed or entirely absent in any form of keloid or in *hypertrophic cicatrix*.

In simple *cicatrix* the papillæ are nearly or entirely obliterated.

Fibroma proper (*hard fibroma*) of the skin is of rare occurrence. Histologically it is seen to be a circumscribed growth, composed of dense fibrous connective tissue interlacing in all directions. Between the fibers are seen small granular connective-tissue cells, which are most numerous in young tumors and gradually disappear in older ones. The tumor contains little or no elastic tissue and but few vessels. A more diffuse hyperplasia of the connective tissue may occur, and include glands, follicles, and vessels in the growth.

Fibroma molluscum (*soft fibroma* ; *molluscum simplex* ; *molluscum pendulum*) is of more frequent occurrence than is hard fibroma. The histologic structure is that of a myxofibroma. The bundles of coarser fibers form a loose network, in the meshes of which are many finer delicate fibers, small spindle-shaped bodies, and a homogeneous myxomatous substance containing small nucleus-like bodies. The myxomatous character is most evident in the center and in young tumors, while the fibrous structure is best developed at the periphery and in old tumors. The epithelial and papillary layers of the skin are rarely involved in the growth, which occurs in the subcutaneous tissue and in the deeper parts of the corium, and is usually sharply bounded from the surrounding tissue. As the tumor grows it pushes out the upper layers of the skin and projects in simple or in lobulated forms. Recklinghausen, Unna, and others believe fibroma molluscum to be a neurofibroma arising from subcutaneous nerve-branches in the form of fine fibrous transparent connective tissue rich in cells which gradually surround glands, follicles, and vessels and replace the normal connective tissue of these parts. The fibrous mass of the tumor may disappear and leave an empty sac of skin, or it may undergo degenerative changes. The growths are occasionally large and form pendulous folds (*fibroma pendulum*, *elephantoid molluscum*). *Dermatolysis* and *cutis lara* are terms often applied to these pendulous tumors, but should be reserved for a somewhat different type of cases, in which the skin may be pulled away from the body in long folds, but when released recoils as would a piece of rubber. In one of these cases, examined histologically, the elastic fibers were normal, but the

connective-tissue bundles were wholly absent, having been converted into a myxomatous mass. Fibromas are frequently associated with feeble mental and physical development, and with pigmentary and other changes in the skin. The etiology is not known, though heredity is recognized in many cases. Closely allied to fibromata are soft warts or *acrochordon*.

Neuroma of pure type is exceedingly rare, and its existence is doubted by many. Most of the growths so named are properly neurofibromas. In Duhring's case the connective-tissue network contained new-formed elements composed of nonmedullated nerve-fibers, some elastic fibers, and vessels with thickened walls surrounded by small lymphoid cells.

Xanthoma has been studied by Touton,¹ Török,² and others. It is apparently a new connective-tissue formation, between the fibers and cells of which are found peculiar xanthoma-bodies, which are cells of an embry-

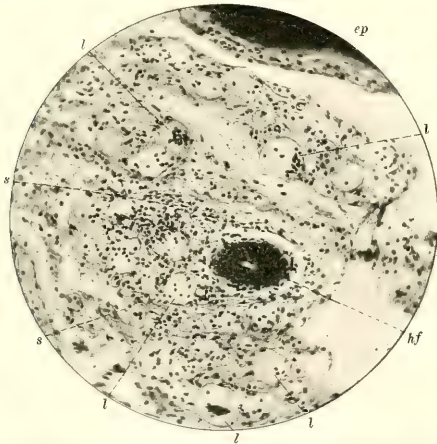


FIG. 387.—Xanthoma planum palpebrarum vulgare: *ep*, epidermis; *hf*, hair-follicle; *l*, large xanthoma-cells; *s*, small xanthoma-cells (Pollitzer's case).

onal or epithelioid type, varying greatly in size and sometimes resembling the giant cells of sarcoma. They possess a distinct membrane, a granular or fibrillated protoplasm, and from one to a dozen or more large round or oval vesicular nuclei. They are more or less infiltrated with fat-granules, sometimes to such an extent that their structure is obscured. They closely resemble developing fat-cells of normal connective tissue, but Török has shown that they never reach the fully developed stage in which the cell contains a single large drop of fat. Moreover, Unna finds these xanthoma-bodies do not respond to stains and to other reagents as do normal fat-containing cells. The bodies are grouped about the vessels and form lobulated masses in the deeper parts of the corium, though they are occasionally found nearly as high as the rete. The epidermis and papillary layer may

¹ *Viertelj. f. Derm. u. Syph.*, H. 1.

² *Ann. de Derm. et de Syph.*, Nov. and Dec., 1893.

show slight thinning, and vacuoles are seen in some of the rete-cells. The new growth is almost entirely confined to the deeper parts of the corium, though portions may extend to the subcutaneous tissue and about the hair-follicles and coil-glands. The sebaceous glands are normal and scanty. The peculiar color of xanthoma is undoubtedly due to the fat-granules, though a yellowish-brown pigment is often found deposited in the deeper rete-cells and in the corium.

The cause and nature of xanthoma are subjects of dispute. Recent observers have described the process as a combination of a new connective-tissue growth with fatty degeneration. Some investigators believe the new growth is preceded by inflammation. Pollitzer¹ has produced strong evidence to show that eyelid-xanthoma is wholly different in structure from multiple xanthoma of the body; that it is not a new growth, but a slow degeneration of the fibers of the orbicularis muscle, which, in a state of granulofatty degeneration with proliferation of nuclei, form the xanthoma-bodies. In a large proportion of cases multiple xanthoma of the body is accompanied by diabetes or by diseases of the liver with jaundice, but the relation of these disorders to xanthoma is not known.

Xanthoma diabeticorum in histologic structure differs from the other forms of xanthoma chiefly in showing more inflammatory changes, more fatty degeneration, less connective-tissue formation, and fewer xanthoma-bodies than in the common varieties. Less than 30 cases have been reported, and in nearly all of these glycosuria was recognized.

Multiple benign cystic epithelioma is a rare disorder that has been described under a variety of names based upon the pathologic findings of different observers. The following description by Fordyce² is generally accepted. Under the microscope the tumors are seen to be "made up of irregularly rounded, oval, and elongated masses and tracts of epithelial cells corresponding to those in the lowermost layer of the epidermis and in the external root-sheath of the hair-follicle. The epithelial masses may be distinct or made up of intercommunicating bands and tracts, in some places resembling coil-ducts. Cell 'nests' are met with as in malignant epithelioma, enclosing horny, granular, and colloid tissue. Colloid degeneration of individual cells is also encountered in the cell-masses. The connective tissue about the cell collections is somewhat condensed, but is not the seat of any inflammatory process."

In origin and in structure these tumors closely resemble true epithelioma, although only two cases so far reported have become malignant (White³). Most of the cases recorded have been in young subjects, and therefore admit a possible later appearance of malignant tendencies. Under the title "*lymphangioma tuberosum multiplex*," Kaposi and others have described a condition which many believe to be identical pathologically and clinically with multiple benign cystic epithelioma, but which Kaposi and his followers maintain is due to a dilatation and new growth of lymphatics in the derma.

Myoma of the skin, in its simple and superficial forms, as distinguished from dartoic and other deep myomas which involve the skin secondarily, is rare, about 15 cases having been reported.⁴ Myomata are limited to the

¹ *Trans. Am. Derm. Assoc.*, 1897.

² *Morrow's System*, iii.

³ *Jour. Cutan. and Gen.-Urin. Dis.*, Nov., 1894.

⁴ Crocker gives a *résumé* of cases to date in *Brit. Jour. of Derm.*, Jan. and Feb., 1897.

corium, are usually multiple and of small size, and are composed chiefly of unstriped muscle-fibers interlacing in various directions. The tumors may be surrounded by a connective-tissue capsule or may contain some elastic fibers. The arrectores pili and the muscle-walls of the vessels are hypertrophied in many of the tumors, thus suggesting the origin of the new growth.

Angioma is a tumor composed of new-formed and dilated blood-vessels. Angiomas of the skin are commonly divided by writers into *naevus vasculosus*, which includes the various congenital forms, and capillary dilatations or telangiectases. Pathologically no sharp dividing line can be drawn between the different clinical forms. Vascular nevi are usually found in the upper part of the corium, and are composed of freely anastomosing, new-formed, and dilated vessels. More or less hypertrophy of connective tissue not infrequently occurs, producing a corresponding firmness in the tumors. Thickening of the horny layer and general epithelial hyperplasia are found in the verrucous elevations often seen in connection with *naevus vasculosus*. In *angioma cavernosum* there are, in addition to enlarged vessels, numerous connecting spaces bounded by connective tissue, the structure resembling that of the corpora cavernosa of the penis. The growth may extend into deeper tissues. Vascular nevi appear at or soon after birth, and after developing to a certain limit, which varies greatly, usually remain stationary for the rest of the individual's life; but they may grow indefinitely, or they may become gangrenous and slough, either spontaneously or, more frequently, as a result of injury.

Telangiectases are usually localized and limited to a few capillaries, but may be diffuse or even generalized. They occur in the neighborhood of tumors, scars, and various other lesions where mechanical pressure may cause dilatation of the vessels. They frequently follow lesions of tuberculosis, lupus erythematosus, syphilis, scleroderma, and other diseases. They may result from any local or general condition which forms long-continued passive congestion of the capillaries. *Rosacea* is the very common form of telangiectasis seen on the faces of men much exposed to the sun and wind.

Angioma serpiginosum is a rare dermatosis, of which but 6 cases have been reported. The histologic examinations of White's case¹ by Darier, Bowen, and Councilman indicate that the growth is a form of angiosarcoma due to some congenital abnormality of the vessels.

Angiokeratoma (*kerato-angioma*), in nearly all of the few cases reported, has followed repeated attacks of pernio. The telangiectatic spots on which the small verrucous elevations have developed show marked thickening of all the layers of the epidermis, with dilated vessels and large spaces filled with blood in the papillæ. Similar spaces containing blood are found in the rete. The condition evidently begins as an angioma, to which is added the hyperkeratosis.

Angioma pigmentosum et atrophicum (*xeroderma pigmentosum*; *atrophoderma pigmentosum*; *melanosis lenticularis progressiva*) is a rare skin disease beginning in the first or second year of life, and undoubtedly due to inherited abnormalities of the papillary layer. It invariably terminates, usually in childhood or young adult life, in malignant growths identical histologically with carcinomas or sarcomas which develop in old age from warts and pigmented nevi. In the earlier stages of the disease the varying clinical phases of pigmentation, telangiectasis, atrophy, and verrucous growths,

¹ *Jour. Cutan. and Gen.-Urin. Dis.*, Dec., 1894.

with their corresponding histologic characters, have been variously interpreted by different observers. In the freckle-like spots there are abundant pigment-deposits in the deeper layers of the rete, in the papillæ, about the blood-vessels and hair-follicles, and in the lymph-spaces. The atrophic points show a complete obliteration of the papillæ, the rete being represented by a few layers of flat polygonal cells. Pigment is absent in both rete and corium. Many follicles, sebaceous glands, and some vessels are obliterated; other vessels are dilated. In close proximity to these atrophic points may be found areas of marked hyperplasia and proliferation of the rete and of the epithelium of the hair-follicles and sebaceous glands. Here the rete-cones extend deep into the corium, and pigment-deposits are abundant in both rete and corium. Complicating the pigmented, atrophic, or hypertrophic lesions, or independently of them, may frequently be found blood-vessels in various stages of dilatation and new formation, a condition which apparently begins with a proliferation of connective tissue and endothelial cells, followed by occlusion of some vessels and resulting dilatation and new formation of others.

Lymphangioma of the skin may be superficial or deep. It is probably always associated with lymphangiectasis, and nearly always with dilatation or new growth of blood-vessels. Simple dilatation of lymphatics may exist, and when superficial may form isolated or grouped vesicles which disappear temporarily under pressure, and which on puncture give exit to a continuous or intermittent escape of lymph, showing them to be connected with the lymphatics. Deep-seated lymphangiectasis, as also the deeper lymphangiomata, either of the cystic or simple tumor varieties, may involve the skin secondarily in inflammatory or in hyperplastic processes, or in the formation of fistulæ. *Lymphangioma* of the skin proper (*lymphangioma circumscriptum*; *lymphangioma cavernosum*; *lymphangioma capillare varicosum*; *lymphangiectodes*; *lupus lymphaticus*) is a rare affection in which vesicles and cysts lined with endothelium form in the upper part of the corium. About the dilated and new-formed lymphatics there may be some cell infiltration and some connective-tissue hyperplasia, and in older cases there is often more or less thickening of the epidermis, producing warty projections over and among the vesicles. In the majority of cases there are dilatation and new growth of blood-capillaries about, and even over, the vesicles and cysts. The changes in the blood-vessels may be slight, or even more pronounced than those in the lymphatics. *Hematolymphangioma* is a fitting title for many of these growths. The causes of lymphangioma are not known, but are probably congenital, as the disease nearly always begins in infancy.

Carcinoma originating in the epithelium of the skin or its appendages is commonly known as *epithelioma*. The attempt to classify carcinoma of the skin according to its origin in the rete or in the epithelium of the follicles or glands is not successful, as it is usually difficult to determine the exact origin of most carcinomas, owing to the fact that the starting point or connecting band may be destroyed by ulceration: or, on the other hand, processes reaching out and involving the glands or follicles may have the appearance of arising in these structures. There is no histogenetic basis for the convenient clinical divisions of cutaneous carcinoma into superficial (or discoid), deep (or tubular), and papillary, aside from the matter of location suggested by the names, nor do these forms remain clinically distinct, but merge one into another.

An important factor in the production of carcinoma of the skin is a long-continued but mild stimulation or irritation of the part, as is seen in the lips, tongue, and cheeks of smokers; in the borders of chronic ulcers; in warts, moles, or small benign tumors that are frequently picked, rubbed, or cut, as in shaving; or in long-continued contact with irritating secretion. Irritation and stimulation of epithelium by chronic inflammation may account in some degree for the occasional appearance of carcinoma in the lesions of lupus and of syphilis or in the margin of a chronic ulcer. Soot, paraffin, tar, and other substances kept constantly in contact with the skin apparently have caused carcinoma. Warts, nevi, and other benign epithelial growths also become malignant. Carcinoma is unusual before the fortieth year of life, but when it does occur in children or young adults is usually rapidly malignant. It occurs most frequently by far on exposed surfaces of the face and hands, about the mucous outlets, and in the genital region, but may occur on any part of the body.

Carcinoma of the skin may be divided into the *lobulated* and the *tubular*, a distinction that cannot always be made, as the two types merge into each other with intermediate forms. In the **lobulated** variety the rete sends down processes which divide and branch in all directions and form lobules of every conceivable shape. The form of the lobules and of the cells may be greatly modified by pressure, the cell sometimes assuming a spindle-shape, making the diagnosis from sarcoma difficult or impossible. The typical lobule, however, has a fairly definite arrangement; the cells of the outer layer are cylindric, stain deeply, and correspond in shape, size, and arrangement to those in the basal layer of the normal rete. Within are cuboidal prickles-cells like those of the normal rete, which toward the center gradually flatten out and lose their nuclei. The central portion is made up of more or less completely cornified cells, which may be arranged in concentric circles, like the layers of an onion, forming epithelial *nests*, *globes*, or *pearls*. The center of the nests may undergo fatty, colloid, or granular changes, or, rarely, may become calcified. In some of the lobules the prickles-cells show no tendency to cornification. The connective tissue into which the growth has penetrated may remain normal or be thickened and infiltrated with cells. It surrounds and supports the lobules and contains vessels, none of which enters the lobules. The invading tumor frequently proves irritating to the surrounding tissues and causes more or less inflammation in them. Fordyce thinks the inflammation due in part to pus infection, and has demonstrated streptococci in the inflammatory tissue.

In the **tubular** variety the epithelial processes are cylindric in form, and extend at varying angles through the cutis and often through the subcutaneous tissue. The outer layers of cells are usually cylindric and stain deeply; the cells within are smaller than in the lobulated form and do not often undergo cornification, nests being uncommon. The character of the cells, together with the fact that the tubules frequently assume shapes suggesting gland-structures, has led many observers to believe that this form of carcinoma always arises in the glands, but proof of such origin is wanting. As a rule, tubular carcinoma is less malignant and less rapid in its course than is the lobular variety. *Rodent ulcers*, described by English authors as a distinct disease, is practically a superficial carcinoma of the tubular variety.

Paget's disease is a superficial carcinoma, which apparently begins as a chronic inflammation of the cutis. It usually occurs on the nipple, but may

appear elsewhere. Kaposi and other observers state that early in the disease the histologic changes are solely those of a chronic inflammatory process. Other observers believe a malignant epitheliomatous growth is present from the beginning.

All forms of carcinoma eventually become the seat of destructive ulceration, although the superficial forms progress slowly and frequently cicatrize in the center or older portions as rapidly as the border advances. The growth may thus show slight activity for years in small areas and without much destruction of even superficial tissue.

Aside from the commoner types described in the preceding paragraphs, three other forms of carcinoma of the skin are recognized by most writers. These may be primary or secondary.

Lenticular carcinoma is a rare condition, most frequently seen on the female breast, the involvement of the skin being in most cases secondary to

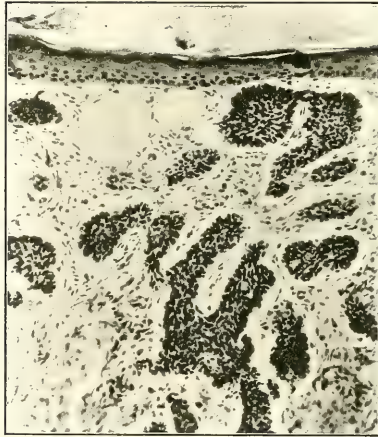


FIG. 388.—Tubular carcinoma from the forehead. $\times 130$. From a photomicrograph (author's case).

mammary carcinoma. The disease may appear on other regions, however, and may be primary in the skin. The small nodular lesions multiply and coalesce to form large infiltrated and sclerotic areas. The skin of the entire chest may thus be rendered hard and leathery or board-like, interfering greatly with respiration—*cancér en cuirasse*. Obstruction of the lymphatics may produce dense edema of the arms. Ulceration in small areas often occurs, but a fatal issue results early from marasmus.

Tuberosc carcinoma is a yet rarer type, which occurs in the form of nodules situated deeply in the skin and subcutaneous tissue. The histologic structure of both the above forms is that of alveolar carcinoma, in which the connective-tissue bands are greatly thickened and sclerosed.

Pigmented or melanotic carcinoma of the skin may take its origin from pigmented moles or other forms of nevi, or from apparently normal skin on any part of the body. The growths may be single or multiple,

secondary foci resulting from metastasis along the lymphatics. The viscera are thus involved early, this form of carcinoma being malignant and rapid in its course.

The differential diagnosis from sarcoma is frequently impossible, either from clinical manifestations or from histologic examination. The great majority of pigmented growths arising from nevi have been described as sarcomatous, but the recent observations of Unna and others have shown that at least some, if not all, of these pigmented tumors arising from nevi have their origin in the epithelial cells, and are therefore carcinomatous.

Sarcoma of the skin is rare. It may be primary in the skin or secondary to the disease in deeper organs. The histologic structure of sarcoma of the skin corresponds to spindle- and round-cell and mixed forms found in other organs. *Fibrosarcoma* and *angiosarcoma* are occasionally seen. Cases of generalized involvement of the skin have been reported in connection with leukemia and pseudoleukemia. Writers commonly divide sarcoma of the skin into pigmented and nonpigmented forms.

Melanotic sarcoma takes its origin in nevi or other pigmented areas; it may arise from apparently normal skin; in about half of the cases its origin is in the uveal tract. The primary tumor may be single and persist for months or years and possibly undergo ulceration before the formation of secondary tumors; or the tumors may be multiple from the beginning. Metastasis occurs through the lymphatics and veins. Dark-brown or black amorphous granules of pigment are found in and about the cells. Melanotic sarcoma is much more malignant and rapid in its course than are the non-pigmented forms, and, according to past reports, is the more frequent form. It is probable, however, that many of the reported cases were in reality pigmented carcinomas, as it is often impossible to make a differential diagnosis either clinically or histologically. Unna and other recent observers believe that all malignant growths arising from pigmented moles and other nevi are carcinomatous.

The so-called **idiopathic multiple pigment-sarcoma** of Kaposi is not, properly speaking, a pigment-sarcoma. The lesions are highly vascular, showing many new-formed blood-vessels with thin walls, which in places are made up of the cells of the tumor. The color of the lesions is due to their vascularity, and in older lesions to pigment left from hemorrhages. No pigment-granules are found either in or about the cells. The progress of the disease is slow, lasting often for years, and, though generally malignant in the end, it occasionally undergoes spontaneous involution and disappears. It is probable that this disease is more closely related to the infectious granulomas than to sarcoma.

Non-pigmented sarcoma may be single or multiple in origin, and may be primary or secondary in the skin. In many cases reported as primary it is possible the original tumor in the deeper tissue was overlooked. Metastases occur sooner or later, involving internal organs, and the disease always progresses to a fatal termination.

PIGMENT ANOMALIES.

The origin, nature, and distribution of the pigment in the normal skin are questions to be decided before the pathology of pigment changes can be determined. Ehrmann, in a recent elaborate work,¹ states that special pigment-cells or "melanoblasts" are formed in the embryo from the mesoderm, which perpetuate themselves throughout the life of the organism and remain independent of all other cells. These cells form pigment from hemoglobin and are united by anastomosing protoplasmic processes, along which the pigment moves in a viscous condition. All free pigment he considers to be detritus. Unna recognizes pigment-cells in the connective tissue, but thinks the so-called pigment-cells in the epidermis are merely lymph-spaces filled with pigment, which he believes to be of two distinct kinds, though he admits the difference has not been demonstrated. Kaposi and Jarisch still think the pigment is formed in the rete.

Congenital excess of pigment is found in pigmentary nevi, in which pigment is found not only throughout the epidermis, but also in the corium. *Congenital absence* of pigment is complete in *albinism* and partial in *leukoderma* (*partial albinism*). Aside from heredity, no causes are known for these defects. *Acquired pigmentation* of the skin from external irritants, or following various skin eruptions, is the result of hyperemia and extravasation of blood. The deposit of foreign matter in the tissues is responsible for the discoloration in *tattooing* and in *argyria*, while in *jaundice* (*icterus*) the skin is stained by the bile-pigment in the circulating blood. In *lentigo* (*ephelis*, *freckle*) there are an intracellular and an intercellular increase of pigment in the basal layer of the rete, caused, in those predisposed, by exposure to the sun's rays or to other unknown (possibly actinic) influences. In *chloasma* the acquired pigmentation may be in small or in large areas, and it appears as a result of a variety of conditions, including *Addison's disease*, exophthalmic goiter, uterine disorders (*chloasma uterinum*), scleroderma, fibroma, tuberculosis, and many other systemic diseases and functional disturbances, as also from the ingestion of arsenic.

In *vittigo* (*acquired leukoderma*) there is a partial or complete absence of pigment in certain areas, about the borders of which the quantity of pigment is frequently greater than normal. The process frequently accompanies central or peripheral nerve lesions, and is probably, like *chloasma*, caused by a disturbance of the sympathetic.

DISEASES OF THE APPENDAGES.

DISEASES OF THE SWEAT-GLANDS.

Hyperidrosis and **anidrosis** are functional disturbances of the coil-glands, which may be congenital in origin or may exist as symptoms of systemic disorders. In such cases the condition is usually general. It is yet a question if complete anidrosis, either general or local (except where the coil-glands are destroyed), ever occurs; but partial anidrosis (more properly hyphidrosis) is frequently seen in regions of the skin affected by dry scaly disease, such as psoriasis or pityriasis. Hyperidrosis of the

¹ "Das melanotische Pigment, und die Pigment bildenden Zellen des Menschen und der Wirbelthiere in ihrer Entwicklung nebst Bemerkungen über Blutbildung und Haarwechsel." *Bibliotheca Medica*, P. ii., Pt. vi.

palms, soles, axillary and genital regions is common, and occurs occasionally on the face, scalp, and other parts of the body. In neither hyperidrosis nor anidrosis have anatomic changes in the glands been found, and no definite cause can be assigned to either; but the conditions are most frequent in connection with nerve disorders and in neurotic individuals. The modification of secretion is probably due to the influence of the nerves on the epithelial cells of the glands.

Bromidrosis is a functional disorder of the sweat-glands, in which the perspiration, either at the time of effusion or soon after, possesses an unusual, usually offensive, odor. It is commonly associated with hyperidrosis, and affects the same regions, but may occur independently of it. Aside from the cases in which uncleanliness favors decomposition of the excretion, the cause is most frequently found in nervous or emotional disturbances. Various micro-organisms can be demonstrated in the fetid sweat.

Chromidrosis is an exceedingly rare condition, in which the sweat is



FIG. 389.—Lesion of miliaria; a vesicopapule: a, center of lesion, clear contents (sweat); b, necrosed rete (Robinson).

colored, usually a dark hue. The causes probably lie in nerve disturbance, but are not definitely known. But few authentic cases are on record. Much more frequently cases of colored sweat occur in which the color is due to the excretion of substances taken into the system, as the green sweat produced by copper, or to accidental or intentional application of dyes to the skin. Red sweat about the axillary and genital regions occurs in connection with concretions (*lepothrix*) about the hairs, and is microbic in origin.

Uridrosis occurs rarely in disease of the kidneys, cholera, and in other grave constitutional disorders, or following the internal use of jaborandi. The amount excreted may be little more than the very small amount often present in normal sweat, or may be so excessive as to leave a flaky or crystalline deposit on the skin.

Hematidrosis occurs as a result of transudation of blood into the coil-glands. *Phosphorescent* or *luminous* sweat has been reported after the ingestion of phosphorus or after a fish diet.

Hidradenitis suppurativa¹ is an inflammatory disease of the coil-glands similar in character to furunculosis. It is most frequent in the axillary and genital regions. The process begins deep in the gland, involves periglandular tissue, and terminates in suppuration and destruction of the gland. The cause is probably a local infection, or some toxic agent excreted by the gland.

Sudamina (*miliaria crystallina*) is a transitory disorder of the sweat-glands occurring in febrile and other asthenic states. Small clear vesicles form in the horny layer, either from occlusion of the duct and consequent

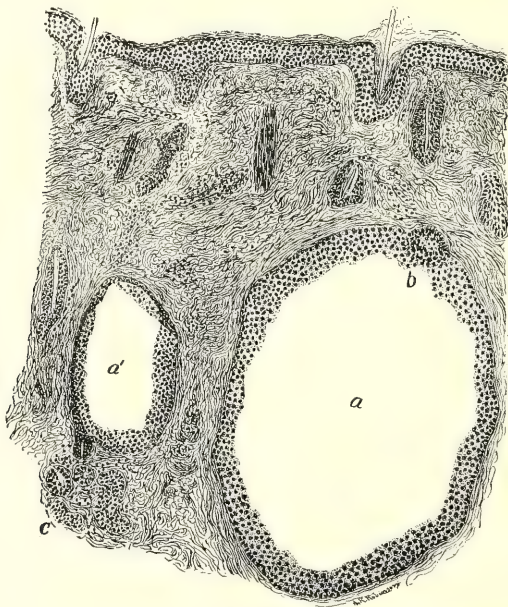


FIG. 390.—Hidrocystoma: *a*, *a'*, large and small cysts; *b*, excretory sweat-duct at place of obstruction; *c*, coil of sweat-gland (Robinson).

retention of sweat; or, according to Robinson, from rupture of the duct and escape of sweat between the horny cells. No inflammatory or other anatomic changes can be demonstrated in the glands, duct, or surrounding tissue. The immediate cause is not known, but probably lies in some change in the epithelial cells lining the duct, and due to high temperature or to defective nutrition.

Miliaria (*miliaria rubra*; *miliaria alba*; *prickly heat*) is an acute inflammatory disease of common occurrence in warm seasons. The cause is found in excessive heat, aided usually by clothing that irritates the skin or prevents free evaporation of the sweat. The vesicles and papules

¹ Pollitzer, *Jour. Cutan. and Gen.-Urin. Dis.*, Jan., 1892.

form rapidly, and are the result of an inflammation in the upper part of the corium and rete, chiefly about the sweat-duct. It is a disputed question whether the vesicles are formed, at least in part, by occlusion and dilatation of the sweat-duct, or whether they are wholly inflammatory in origin. The sweat-glands show evidences of great activity, but are otherwise normal.

Hidrocystoma is a somewhat rare disease of the coil-glands in which more or less numerous discrete, clear, deep-seated vesicles, resembling sago-grains, appear usually on some part of the face. The vesicles are formed by dilatation of a portion of the sweat-duct in some part of the corium. They contain sweat and some granular matter, and are lined by several layers of epithelial cells, showing that the dilatation is not merely passive. The cause of the disease is not known, but is probably due in part to the associated hyperidrosis and in part to some defect in the tissues. The other structures of the skin are normal.

DISEASES OF THE SEBACEOUS GLANDS.

Seborrhea is commonly described by writers in two forms, the oily and the dry.

Seborrhea oleosa is due to an excessive functional activity of the fat-producing glands, as a result of which the skin is kept constantly greasy and oily. This form of the disease is frequently associated with the dry form, or complicated by inflammatory processes, producing some of the conditions described under Seborrhoic Dermatitis. No anatomic changes have been demonstrated in the sebaceous or coil-glands; and while the latter probably secrete fat, the fact that they do so has not definitely been established.

Seborrhea sicca is thought by Unna, Elliott, and others to be always inflammatory and microbic in origin, and by them is considered identical with seborrhoic eczema. The followers of Hebra and Kaposi believe that the process is often non-inflammatory, and due to a disturbance in the functional activity of the sebaceous glands, as a result of which the epithelial cells lining the glands are but partially transformed into sebum and are deposited on the skin, mixed with fat and with other epithelial cells. In mild cases there is little more than a slight exfoliation from the surface (*pityriasis simplex*, *dandruff*), but the quantity of cells and fat may be so great as to cover the surface with thick oily scales. Long-continued seborrhea results in atrophy of hair-papillæ and permanent alopecia. The causes of seborrhea are not definitely known, as it occurs in persons who are apparently well in every other respect, but it is frequently associated with digestive disturbances, anemia, or malnutrition from any cause. Locally, any condition which keeps the surface warm or more or less constantly congested favors the development of seborrhea. Many of the dry and inflammatory forms seem to be due to micro-organisms and to be feebly contagious (see Seborrhoic Dermatitis).

Sabouraud¹ finds in every form of seborrhea a very small, short bacillus which is easily stained by Gram's method, and which is always situated in the upper part of the hair-follicle above the opening of the sebaceous gland. The bacilli are found in pure state, within a cocoon-shaped mass of fatty and horny matter, and are easily cultivated.

¹ *Ann. de l'Inst. Pasteur*, p. 134, 1897.

Asteatosis is a term applied to complete or partial absence of sebaceous matter secreted by the skin. The condition is usually local and the result of other disorders, especially of dry scaly disease, such as psoriasis, pityriasis rubra pilaris, ichthyosis, etc. It is seen in senile and other atrophic conditions of the skin. It may be produced by constantly removing the normal secretion, as occurs in laundresses and others whose hands are constantly in soapy or strongly alkaline solutions.

Comedo is a plug or mass of sebum and epithelial cells occluding the duct of a sebaceous gland. The central mass contains cholesterin, lanugo-

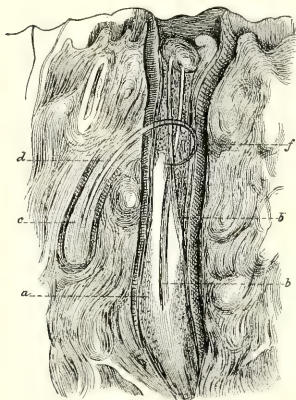


FIG. 391.—Section of a comedo: *a*, excretory duct of a sebaceous gland filled with a comedo; it contains also two small hairs with brush-like inferior extremities; into it opens a small hair-follicle (*c*), whose contained hair (*d*), after touching the opposite wall of the duct, curves downward at *f* (Kaposi).

hairs, fat, and cells that have undergone partial fatty metamorphosis, and is surrounded by concentric layers of horny cells. The external end of the plug is frequently dark or even black, due to the collection there of dust, dirt, etc., or, according to Unna, to the presence of a special pigment—*ultra-marine*. Unna states that the formation of the plug begins with a parakeratosis on the external surface, which closes the duct. Biesiadecki showed that the follicles of lanugo-hairs frequently form obtuse or right angles with the ducts of the sebaceous glands, and suggests that the end of the hair extending into the duct incites epithelial hyperplasia, and thus produces the layers of cells surrounding the central mass. Other observers think that sluggishness of the glands allows the sebum to dry in the duct, and by mechanic irritation to excite the cell proliferation. The disease occurs most frequently at puberty, when there is

the most active growth of the glands and of hairs. While it may occur in persons who are in good general health, it is more frequently seen in those suffering from constipation and other disorders of digestion, or from other systemic disturbances.

Milium is a pinhead-sized, or smaller, mass found in a sebaceous gland as a result of occlusion of the duct. The mass consists of a central portion containing fat and cells, which is surrounded by concentric layers of horny cells and is enclosed in a capsule, so that the entire body may be easily enucleated. The causes of obstruction of the duct are usually unknown, but are traceable sometimes to mechanical injury or to scars.

Steatoma (*atheroma*; *sebaceous cyst*; *wen*) is a cyst of a sebaceous gland, composed of connective tissue of varying density, within which are concentric layers of epithelial cells, and a central mass which may be granular, semisolid and cheesy, or fluid and milky, or even purulent. The contents include fat, epithelial debris, cholesterin, and fine hairs. Török found true papillæ in some cysts, and with Chiari believed them to be

dermoid cysts, and therefore embryonic in origin. The majority of writers class them as mere retention cysts. The causes of retention are probably similar to those which produce comedo and milium.

Adenoma sebaceum is a somewhat rare disease of the sebaceous glands in which pinhead- to pea-sized sessile, round or oval tumors form chiefly on the forehead, chin, and along the furrows beside the nares. The acquired form is covered by normal epithelium. The congenital vary in color from yellowish white to brownish red, and are frequently associated with minute vascular dilatation. They are found most frequently in individuals of defective mental development. Histologically there is marked enlargement of the sebaceous glands. Other changes reported by different observers are interpapillary hypertrophy (Pringle), cysts of both sebaceous and coil-glands (Balzar), and hyperplasia of coil-glands and hair-follicles (Crocker).

Acne vulgaris is an inflammation of the sebaceous glands and periglandular tissue, including commonly the hair-follicles. The inflammation may be superficial and limited to the tissue about the duct; or it may be deeper and involve the gland proper together with the hair-follicle and surrounding tissue; or it may involve several glands and the intervening tissue in the formation of a small abscess. The inflammation usually goes on to suppuration and destruction of the gland and often of the hair-follicle, but may be of mild type and undergo involution without suppuration or loss of tissue. The various clinical appearances of acne depend upon the site and varying intensity of the process. *Indurated acne* is a term applied to that form in which the lesion is deep-seated, indurated, and shows little tendency to spontaneous rupture and discharge of pus.

Acne occurs most frequently at puberty, at a time when the glands are actively developing and when there is more or less constitutional disturbance. It is frequently due to constipation and other derangements of digestion, to sluggishness of the general physical activity, to the ingestion of certain articles of food and of drugs, to exhaustion, and to various disorders of other organs. In the majority of cases the acne lesion is formed about a comedo or other foreign body which obstructs the duct and acts as a mechanical or chemical irritant. The lesions may be produced through the irritating action of substances excreted by the glands. Pus-cocci and other micro-organisms are found in the lesion, and Unna and others describe a special bacillus which they think responsible for the disease.

Rosacea begins as a transitory, then persistent, passive hyperemia of the superficial capillaries. Paresis, dilatation, and hypertrophy of the capillaries and deeper vessels follow. As a result of congestion there is increased activity of the sebaceous glands, producing oily seborrhea. Later, proliferation and inflammation of the glands add acne lesions, and the condition is known as *acne rosacea*. In the later stages there are chronic edema and hyperplasia of the connective tissue and of glands, producing a thickened and nodular formation known as *rhinophyma*.

Varioliform acne presents small circumscribed inflammatory lesions of the skin in which there is central necrosis. Further than this, little is known of the pathology or etiology of the disease. Different observers have located the origin of the process in the sebaceous glands, in the hair-follicles, in the perifollicular tissue, and in the coil-glands. It is probably a local infective process.

DISEASES OF THE HAIRS AND HAIR-FOLLICLES.

The abnormal pigment-changes in the hair are imperfectly understood. They are probably due in great part to neurotic influences. Inheritance, nervous exhaustion, debilitating diseases, and nerve-shock are prominent features in the etiology. *Canities* may rarely be inherited, but is usually an acquired condition. It is common in connection with other senile changes, but may occur earlier in life. The whitening of hair is produced not only by the loss of pigment, but also by the presence of air in the cortex. In cases of rapid blanching of the hair after fright or other nervous shock the pigment is hidden by a rapid accumulation of air between the cells of the cortex. Discoloration of the hair occurs in workers in copper, cobalt, and indigo, and from local contact with dyes, etc. A change in color may occur after severe illness with temporary loss of hair, and has been reported after profuse sweating, after the hypodermic use of pilocarpin (Prentiss), and after exposure to cold and exhaustion (Griffith).

Hypertrichosis is a deformity rather than a disease. It is simply a growth of hair that is abnormal in quantity or in location, and may be congenital or acquired. Rarely, when congenital, it is practically universal, covering all the body except the palms, soles, last ungual phalanges, prepuce, glans penis, upper eyelids, and borders of the lips. More frequently it is localized. The causes are not well known, but among them may be named heredity and a precocious, perverted, or arrested function of the generative organs. Locally the condition may be encouraged by applications, pressure, or anything that produces a congestion of the parts.

Alopecia is divided by Jackson into four varieties: *Alopecia adnata*, *alopecia senilis*, *alopecia prematura*, and *alopecia areata*. In all forms the disease is most common on the scalp, but may appear on any or all of the hairy parts of the body.

Congenital alopecia is rare, and is usually accompanied by defects in the teeth and nails; the causes are unknown, but in some cases it is hereditary.

Alopecia senilis occurs in common with other senile changes, and is probably due to atrophy of the hair-papillæ.

Alopecia prematura, aside from cases that result from, or are symptoms of, fevers, syphilis, erysipelas, ringworm, and other systemic or local disease, may appear as an idiopathic affection. Any systemic condition which interferes with general nutrition, and therefore with the nutrition of the hair, necessarily favors, if it does not produce, alopecia. Heredity is apparently a prominent factor in many cases, but frequently no cause is recognized. In the great majority of cases alopecia is preceded by "dandruff" or some other form of seborrhea or seborrheal dermatitis. Unna, Sabouraud, Elliott, and others believe that alopecia is almost invariably due to microbic infection of the hair-follicles and sebaceous glands, and is but a part of the seborrheal disease. The micro-organisms are those described under Seborrhea and Seborrheic Dermatitis. Sabouraud¹ has produced alopecia in sheep, rabbits, and guinea-pigs by the inoculation of toxins produced in pure cultures of his short bacillus of seborrhea.

Alopecia areata has been described by most writers as a trophoneurosis, and it is difficult to account for some cases of rapid and extensive alopecia on any other ground. Moreover, the alopecia has followed in many instances

¹ *Ann. de Derm. et de Syph.*, March, 1897.

some nerve injury, shock, or other disturbance of the nervous system. On the other hand, the parasitic theory accounts very satisfactorily for many of the limited and circumscribed cases. A number of epidemics of the disease have occurred, and other evidences of contagion have been noted. Different observers have described different micro-organisms in a few cases. Sabouraud¹ reports that he finds constantly in the early stage of the process the same bacillus in the upper third of the hair-follicle that he has described in connection with seborrhea. In succeeding stages the bacilli have disappeared, but leave evidences of toxic influences upon the tissue, in the form of achromia of the basal layer of the rete, intense diapedesis of lymphocytes and mast-cells, and progressive atrophy of the hair-follicles. With pure cultures he has succeeded in producing typical areas on the calf, rabbit, and guinea-pig. He thinks alopecia areata might well be considered an acute form of oily seborrhea. The changes in the hairs themselves are regressive in character, and vary with the time required for the atrophy of the papillæ. The earlier researches of Giovannini and Robinson showed inflammatory changes about the follicles, which both observers believed were secondary. Finally cases occur which are plainly associated with ringworm of the scalp, and there are observers who believe that alopecia areata is an acute form of trichophytosis.

Alopecia decalvans or *folliculitis decalvans* is a general term applied collectively to several somewhat rare and similar diseases which have been described under various names, chiefly by French writers. The disease is essentially a destructive inflammation of the hair-follicle and surrounding tissue, resulting in loss of hair and in destruction of the follicle, with the formation of scar-tissue. The lesions show a tendency to grouping, and spread slowly during months or years. The condition is most frequent on the beard and scalp, but may occur on other parts, and is due probably to a local infection of the follicles.

Dermatitis papillaris capilliti, or *keloid acne*, is described by Kaposi as a chronic inflammation of the derma, resulting in hyperplastic connective tissue, and in destruction of the sebaceous and coil-glands, and later of the hair and hair-follicles. Some writers class this disease with folliculitis decalvans. It is always situated on the back of the neck, from which part it may spread to the vertex.

Atrophy of the hair is due usually to some systemic condition which interferes with the nutrition of the hair. It occurs also as a symptom of local disease, such as eczema, psoriasis, and seborrhea. In the common form of the disease the hair becomes dry, lusterless, and splits at the ends or through a greater portion of the shaft, producing the condition known as *fragilitas crinium*. Of the rare forms of atrophy may be mentioned *trichorrhexis nodosa* and *monilethrix*. In the former the hairs, usually of the beard, present swellings or nodes through which the hair easily fractures, leaving frayed-out ends. Some observers believe this disorder to be parasitic in origin. Monilethrix is generally congenital and frequently hereditary. The shaft shows nodes representing the normal part of the hair and constrictions through which the hair fractures. *Plica polonica* is simply a mass of matted hair due to filth, pediculi, and neglect. *Piedra* is found in the United States of Colombia only. The small stony nodules which form on the hair of the scalp are probably due to a fungous growth. *Beigel's disease* is a fungous

¹ *Trans. Internat. Cong. of Derm.*, London, 1896.

growth found on artificial hair. *Tinea nodosa* is described by Morris and Cheadle as a fungous growth forming nodular concretions on the hair, giving it an irregular appearance and rendering the hair fragile. *Lepothrix* is found on the hairs of the axillæ and scrotum, in the form of lobulated or nodular concretions along the shaft of the hairs, which are dry, rough, brittle, and loosened in their follicles. The condition is frequently associ-

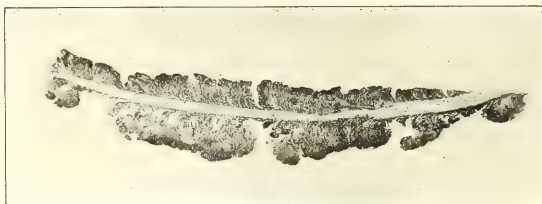


FIG. 392.—*Lepothrix*. From a photomicrograph (author's case).

ated with "red sweat," and is due to a short bacillus which penetrates the cortex of the hair and there multiplies. The concretions are made up chiefly of a homogeneous cement resembling chitine.

DISEASES OF THE NAILS.

Diseases of the nails are for the most part the result of trophic changes in the matrix, which in turn are dependent upon systemic disease, as in syphilis, or upon other local disease, such as eczema or psoriasis.

Overgrowth of the nail (*onychauxis*) may be simple, but is usually accompanied by a change in texture and color of the nail substance, and is frequently associated with atrophic changes. The nails thus become thickened, rough, uneven, porous, friable, often partially elevated and loosened from the nail-bed, lusterless and opaque, or grayish or dirty yellow in color. The nail may become bent and twisted, or curved over the finger-tips, producing a condition known as *onychogryphosis*.

In **atrophy** of the nail the nail proper may be simply thinned and softened, but is more commonly marked by furrows and ridges, either transverse or longitudinal, or by numerous small pits or depressions, and is brittle, split, or fragile, and often discolored.

Hyperkeratosis of the nail-bed may occasionally produce a mass of imperfectly keratinized cells which raise the nail from the bed, and which frequently become softened and foul-smelling, probably as a result of secondary infection.

These changes in the nail and its bed occur most frequently in connection with syphilis, psoriasis, and eczema, but are found often in leprosy, tuberculosis, myxedema, acromegaly, neuritis, and in many diseases of the nervous system, and may result in temporary or permanent loss of the nail.

Shedding of the nails may occur in syphilis, alopecia areata, diabetes mellitus, hysteria, and in many neurotic conditions; subungual ecchymosis may occur from injury or other cause and produce a blood-clot that will gradually lift the nail from its bed and cause it to fall.

The trophic changes may be associated with chronic inflammation of the matrix or of the nail-fold. Inflammation of the matrix (**onychia**) and of the nail-fold and surrounding tissue (**paronychia**) occurs in acute form from injury (as in ingrowing toe-nail) or from local infection, and is most frequent in the tuberculous. The degree of inflammation varies from mild to destructive forms, in which the nail and a portion of the surrounding tissue may be permanently destroyed.

Congenital absence and deformities of the nails are of infrequent occurrence, and are usually associated with defects in development of the hair and teeth. Nicolle and Hallipré,¹ and C. J. White² have reported cases in which such deformities were transmitted through several generations.

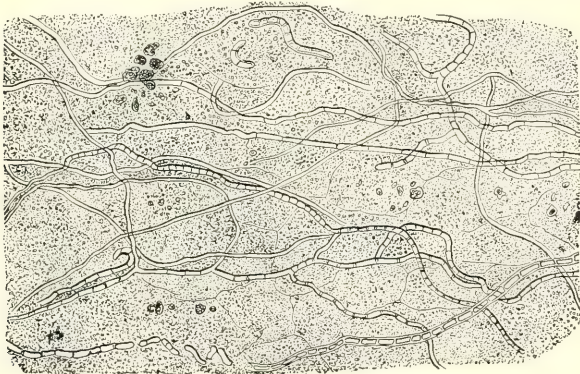


FIG. 393.—Onychomycosis trichophytina (Corlett).

White spots, lines, bands, or patches are frequently seen in the nails, and are due to the presence of air between the cells. The condition is known as **leukopathia unguis**, and is due to slight injury or to interrupted nutrition, such as occurs during fevers and other debilitated conditions. Periods of interrupted nutrition are sometimes marked on the nails by transverse furrows. In **onychomycosis** the nail proper is the seat of favus or ringworm, the spores and mycelium being found in spaces between the horny cells.

¹ *Ann. de Derm. et de Syph.*, Aug., 1895.

² *Jour. Cutan. and Gen.-Urin. Dis.*, June, 1896.

THE EYE.

Development and Normal Structure.—It is proposed, in this introductory section, to review briefly such points in regard to the development, histology, and blood-supply of the various parts of the eye as are essential to the understanding of the pathologic processes affecting them.

Beginning with the cornea, we find that its parenchyma is formed from a sheet of mesoblastic tissue lying just beneath the layer of epithelium composing the primitive epiblast. At first this mesoblastic tissue consists of indifferent formative cells, but these soon become spindle-shaped, and then give rise to the numberless fibrillæ which make up the bulk of the cornea. Groups of fibrillæ are cemented together into bundles, and bundles that run parallel and in the same plane are, in their turn, cemented into lamellæ, superimposed to the number of forty or more to make up the thickness of the cornea.

Between the lamellæ the original formative cells remain permanently as flattened stellate corpuscles, the fixed corneal corpuscles, which again may play an active part in regenerative processes. Between the lamellæ, furthermore, there are systems of fine lymph-spaces for the nutrition of the cornea, since the numerous blood-vessels existing in the latter in its fetal state are reduced later to a looped vascular network about its margin.

A thin portion of the anterior layer of the parenchyma of the cornea is condensed to form the structureless membrane of Bowman, which serves as a basement membrane for the anterior epithelium. Posteriorly an endothelial layer spreads over the cornea and secretes the resistant elastic membrane of Descemet. The membrane of Descemet extends nearly to the periphery of the cornea, and there gives place to the ligamentum pectinatum, a loose-meshed structure occupying the angle of the anterior chamber, through which the aqueous humor filters, to be taken up by the vessels of the sclera. The endothelium lines the anterior chamber, resting in a single stratum upon the membrane of Descemet, whence it continues in a broken layer over the inner surface of the ligamentum pectinatum and through the spaces in its substance, and finally passes over, in a broken layer still, to the anterior surface of the iris.

The sclera is similar in structure to the parenchyma of the cornea, except that the scleral bundles interlace and run in various directions, their arrangement being for strength, whereas in the more regular arrangement of the corneal bundles strength is sacrificed to transparency. When the cornea becomes inflamed, it having no blood-vessels of its own, the infiltrating leukocytes are attracted from the vessels of surrounding parts.

The lids are formed from folds composed of mesoblastic tissue covered with epithelium which are thrown out above and below the cornea, and grow toward each other until they finally meet in the median line and are temporarily united. The epithelium on the outer surface of the lids then grows thicker to form the epidermis, and at the lid margins dips in to form

the follicles for the lashes, while just behind the lashes the Meibomian glands develop as long epithelial cylinders pushing in from the lid margin and later becoming branched and finally hollowed out so as to form tubules. In their growth the epithelial cylinders compress the surrounding mesoblastic tissue, which in time forms the dense fibrous tarsus in which the Meibomian glands lie embedded. Anterior to the tarsus the fibers of the orbicularis muscle are laid down in bundles, and anterior to these is the loose subcutaneous tissue of the lid.

The conjunctival sac is at this time a closed sac lined with a continuous layer of epithelium, which soon begins to differentiate. On the inner surface of the lid the epithelium consists of a double layer of columnar or cuboidal cells, bound tightly down to the tarsus by a very thin layer of lymphadenoid tissue. In continued inflammation this tarsal conjunctiva is thrown up into folds like the papillæ of the skin. The retrotarsal portion of the conjunctiva has a thicker epithelium, and is so folded that it possesses great mobility. Underlying it is considerable loose lymphadenoid tissue with many blood-vessels, and in inflammations this tissue becomes very much swollen and infiltrated. On the eyeball the epithelium is thicker and more of the pavement variety. It is bound down to the sclera by a thin layer of elastic tissue, which near the surface of the sclera is more compact and vascular, being known as the episcleral tissue. This episcleral tissue is subject to independent inflammation, while the bulbar conjunctiva proper is more prone to simple edematous swelling or chemosis. Near the cornea the epithelium of the bulbar conjunctiva comes to resemble that of the cornea, which is quite thick, consisting of a basal layer of columnar cells, a middle layer of cuboidal cells, and a superficial layer of flattened cells which grow flatter and more horny as they approach the surface. The deeper cells are the more active in proliferation.

The shape of the growing eyeball is conditioned by the secondary optic vesicle, about which the mesoblastic tissue is moulded to form the outer ocular membranes—a vascular layer next the vesicle-wall giving rise to the connective-tissue portions of the iris, ciliary body, and choroid, and an outer nonvascular layer giving rise to the denser sclera.

The wall of the secondary optic vesicle itself consists of two layers of neural epithelium, the outer of which becomes the pigment-epithelium, which extends as a single uniform stratum of pigmented cells from the optic nerve entrance forward to the pupillary margin of the iris. In the inner layer of the vesicle-wall, however, a differentiation takes place, leading to the evolution of its three distinct divisions: the pars iridis retinæ, the pars ciliaris retinæ, and the retina proper. That is, on the posterior surface of the iris the inner layer of the secondary optic vesicle forms a second or posterior stratum of pigmented cells (pars iridis retinæ). At the ciliary margin of the iris these cells lose their pigment and continue over the ciliary body (pars ciliaris retinæ) as cuboidal cells, becoming more columnar as they pass back, until finally at the ora serrata they abruptly pass over into the stratified retina.

The connective-tissue portion of the iris arises from a sheet of mesoblastic tissue thrown out over the double pigment layer and developing simultaneously with the latter. It consists of a rather loose tissue covered with a broken layer of endothelium, and containing, near the pupil, the sphincter pupillæ muscle.

The arteries of the iris, which have unusually thick walls, spring from the major vascular circle in the ciliary body and extend radially toward the pupil; just before reaching the pupillary margin they break up to form the minor vascular circle of the iris.

The ciliary body has its inception in a folding of the vesicle-wall antero-posteriorly, with a corresponding indipping of the mesoblast; then a lateral plaiting of this fold produces the ciliary processes, the purpose of which is to increase the surface secreting the aqueous humor. The bulk of the ciliary body comes to consist of the ciliary muscle, but resting on its inner surface and filling the ciliary processes is a spongy tissue, continuous with the iris and receiving a rich blood-supply from the same vascular circle. It is this superficial spongy tissue that is chiefly affected in inflammations, the interstitial tissue of the ciliary muscle often remaining uninvolved.

At the posterior end of the ciliary body this tissue passes over into the choroid, and is transformed here into a coarse-meshed scanty network for the support of the vessels which largely make up the choroid. The choroidal vessels are arranged in three superimposed layers: An outer layer of large vessels, mostly veins, which empty into the *venæ vorticosæ*; a middle layer of medium-sized vessels, mostly arteries, given off from the posterior ciliary arteries; and an inner layer of close-meshed capillaries. The chief function of the choroid is to nourish the outer layers of the coextensive retina, and it is consequently most richly supplied with blood-vessels in the neighborhood of the macula lutea, where the outer or perceptive layers of the retina exercise their highest functional activity.

Between the capillary layer of the choroid and the pigment-epithelium there is an elastic membrane, the lamina vitrea, commonly regarded as part of the choroid, but in reality a cuticular secretion of the pigment-epithelium. This membrane adheres tightly to the choroid, and the pigment-epithelium has a firmer attachment to it than to the layer of rods and cones. Thus it happens that in most cases of simple detachment of the retina the pigment-epithelium remains in place, with the choroid.

The primitive retina consists of a thick layer of neural epithelial cells, bounded on either surface by a cuticular membrane, called respectively the *membrana limitans externa* and *limitans interna*. The cells early begin to differentiate, and fall into two main groups, those which are to be true nerve-elements and those which are to be supporting elements. The supporting elements come to consist, first, of Müller's fibers—thick nucleated columns extending transversely through the retina from the *limitans externa* to the *limitans interna*, and spreading out into a cone-shaped base attached to the latter; second, the two longitudinal reticular layers (with their spongioblasts) separating the three nerve-cell layers; and, third, a few true neuroglia-cells in the nerve-fiber layer. The nerve-elements begin with the nerve-fiber layer, which lies just within the *limitans interna*, and is composed of axis-cylinders which are mainly long processes of the large ganglion-cells composing the next outer layer. External to the ganglion-cell layer comes the inner reticular layer, then the inner nuclear layer, then the outer reticular layer. The inner nuclear layer consists chiefly of small bipolar ganglion-cells with one process ending in a terminal arborization in each reticular layer. This much of the retina is nourished by the retinal vessels, and is known collectively as the cerebral or conducting stratum. The outer nuclear layer and the rod-and-cone layer are nourished by the capillaries of the

choroid, and are known as the modified neuro-epithelial or perceptive stratum. In the fetus the cells of the outer nuclear layer have an inner process ending in the reticular layer, and an outer process ending at the *membrana limitans externa*; but later this outer process pierces the *limitans externa* and projects into the pigment-epithelium as a rod or cone. After this extension has taken place the cells of the outer nuclear layer are regarded as nucleated rod- or cone-fibers, the fiber and the rod or cone being portions of a single nerve-element. The *limitans externa*, after being perforated by the rods and cones, is merely a cribriform membrane, while the *limitans interna*, after the cone-shaped bases of Müller's fibers have acquired attachment to it, seems to consist only of these bases, and is commonly so described. Idiopathic inflammations of the retina involve chiefly its inner layers, while inflammations of the choroid affect chiefly the outer layers.

The optic nerve is first represented by a solid epithelial stalk connecting the secondary optic vesicle with the second cerebral vesicle. The ganglion-cells of the retina then throw out long processes or neuraxones, which run centripetally among the epithelial cells of the optic stalk to reach the brain; at the same time neuraxones from cerebral neurocytes run centrifugally through the optic stalk to end in the retina. The epithelial cells of the optic stalk then become transformed into stellate neuroglia-cells, which bind the axis-cylinders together into bundles. A mesoblastic sheet about the optic stalk divides into two concentric layers, which form respectively the dural and the pial sheath; and between the two is the intervaginal lymph-space, which is continuous with the subdural space. From the inner or pial sheath vascular membranes push in among the neuraxones of the nerve and form connective-tissue septa which divide the nerve into coarse bundles. Finally the neuraxones take on a medullary sheath as far as the lamina cribrosa, beyond which the fibers enter the optic disk as naked axis-cylinders.

The lens is developed from an epithelial sac formed by a pushing-in of the epiblast. The epithelial cells of the margin of the sac secrete the elastic capsule, and the posterior cells of the sac grow out into lens-fibers, while the anterior cells remain as the subcapsular epithelium. In pathologic states the epithelium proliferates and the fibers degenerate.

When the secondary vesicle is first formed, its cavity is filled almost entirely by the lens. The little remaining space is occupied by a loose vascular mesoblastic tissue which pushes into the vesicle through its inferior cleft. As the vitreous cavity grows larger the vessels of the ingrown mesoblastic tissue arrange themselves into two systems, one lying near the vesicle-wall and the other passing directly forward to the posterior pole of the lens. Connective-tissue elements other than thin-walled vessels then disappear almost entirely, the vitreous being a gelatinous body, delicately fibrillated, and formed from liquids transuded from the fetal blood-vessels. Before birth the vessels disappear and there remain only a few scattered cells, which are probably for the most part leukocytes, although some have the branched forms of connective-tissue cells.

The vitreous may become infiltrated passively in exudative inflammations of the vascular membranes of the eye, or it may, when infected primarily, become infiltrated with leukocytes which are attracted toward the infective substances from the vessels of surrounding parts.

THE CONJUNCTIVA.

THE ACUTE INFLAMMATIONS WITH EXUDATION.

For convenience of pathologic description we may group together all the acute infectious conjunctival inflammations that are characterized by discharge and simple inflammatory infiltration of the conjunctiva without permanent changes in the tissues. The process is the same in all, and the clinical distinction depends mainly upon the nature of the discharge. In the affected conjunctiva the vessels are congested, while the lymphadenoid tissue is edematous and infiltrated with leukocytes. The superficial epithelial cells become loosened and are cast off. The discharge consists of serum, mucus, epithelial cells, leukocytes, and fibrin, in varying proportions. The micro-organisms which cause the inflammation lie in and among the cells of the discharge, and among the superficial epithelial cells of the conjunctiva, but they never extend deeper; the toxic substances which they secrete, however, are dissolved and diffused into the deeper tissues, and there bring about processes of inflammation.

Many varieties of micro-organisms are found on the normal conjunctiva in small numbers, and their development is favored by injuries, dust, inflammations, and the presence of secretions. In general, such micro-organisms are of two categories: those which are not pathogenic under any circumstances, and those which are innocent while the conjunctiva is unbroken, but pathogenic when introduced into the tissues. Of the latter, the staphylococcus and the tubercle bacillus are good examples. In a third category are micro-organisms which are uniformly pathogenic even on the unbroken conjunctiva. Such is the gonococcus, whose relation to specific purulent conjunctivitis is definite.

Acute epidemic conjunctivitis may be caused by a variety of micro-organisms, the same clinical picture being brought about in different regions and in different epidemics by altogether different microbes. The micro-organisms which are known to cause acute catarrhal conjunctivitis are as follows: 1. The Weeks bacillus; 2. The *Micrococcus lanceolatus* (*pneumococcus* of Fränkel); 3. The streptococcus; and 4. A diplobacillus, described by Morax and later by Axenfeld.

The ordinary epidemics of acute catarrhal conjunctivitis are due usually to the Weeks bacillus, to the pneumococcus, or more rarely to the Morax diplobacillus, though the inflammation caused by the last is usually subacute. Sporadic cases, more or less typical, may occasionally be caused by the diphtheria bacillus alone or together with the streptococcus, or by a gonococcus of attenuated virulency.

The pneumococcus is frequently present on the normal conjunctiva, and is almost invariably found in small numbers in the secretion of the conjunctiva when influenced from other causes. It is undoubtedly the cause of many epidemics of acute catarrhal conjunctivitis, especially in children, and of a more chronic form in adults.

The diphtheria bacillus resembles the pseudodiphtheria or xerosis bacillus both in its appearance in preparations and in its growth in cultures, so that inoculation in animals is the only sure test of its virulency. The pseudodiphtheria bacillus may be found in small numbers on the healthy conjunctiva. It may proliferate and be present in large numbers in the

secretion caused by other micro-organisms, and particularly in the fibrinous membranes following trauma. The genuine diphtheria bacillus may cause a catarrhal inflammation, a croupous or pseudomembranous inflammation without constitutional symptoms, and a true diphtheria with necrotic patches and marked systemic disturbance. In the severe cases the streptococcus also is usually present, and the disease must be regarded as due to a mixed infection.

The gonococcus, in secretion, appears as a diplococcus, the two elements of which are biscuit-shaped and lie closely side by side (Fig. 394, I.). After division the elements appear in groups of four, which are characteristic. The gonococcus will be found for the most part within the leukocytes, where

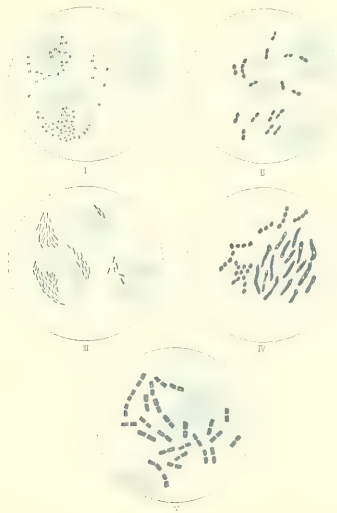


FIG. 394.—Micro-organisms found in the secretion of acute conjunctivitis: I., gonococcus; II., pneumococcus; III., Weeks' bacillus; IV., diphtheria bacillus and streptococcus from culture of diphtheritic membrane; V., Morax-Axenfeld diplobacillus. $\times 1200$.

it proliferates until it occupies most of the cell-body. The pneumococcus also is a diplococcus, its two oval elements giving it, particularly when its capsule is well marked, a lanceolate form (Fig. 394, II.). It is found scattered among the cells and in small groups within the cells. It can hardly be mistaken for the gonococcus, Gram's method of staining being taken by the pneumococcus, but not by the gonococcus. Since the pneumococcus has a tendency to arrange itself in rows of four or more elements, it may at times be mistaken for the streptococcus, but the diagnosis is easily made from cultures. The Weeks bacillus is a very small bacillus which is found in great numbers both among and within the cells (Fig. 394, III.). The diphtheria bacillus is a large micro-organism of varying form and size (Fig.

394, IV.). It frequently contains points which do not take the stain. Its characteristics in a given case can be learned only by cultivation and inoculation into animals. While it differs morphologically from the Weeks bacillus to such an extent that a confounding of the two is not likely, they may be definitely distinguished by employing Gram's stain, which leaves the diphtheria and pseudodiphtheric or xerosis bacillus colored, but removes the color from the Weeks bacillus.

The Morax-Axenfeld diplobacillus is a thick bacillus arranged in pairs, and does not stain by Gram's method. It should be borne in mind in examining secretions that xerosis bacilli and pneumococci in small numbers frequently appear in secretions caused undoubtedly by the Weeks bacillus or by the gonococcus. The diagnosis depends in some degree upon the numbers of a particular micro-organism present.

THE CHRONIC NEOPLASTIC INFLAMMATIONS.

Papillary Conjunctivitis.—The normal tarsal conjunctiva is closely adherent to the tarsus, and the epithelial layer is smooth, except near the upper tarsal margin, where it is thrown into folds. The folds are often almost contiguous, and the epithelium dipping down into the depressions between them suggests gland-structures, known as Henle's glands. After any long-continued severe catarrhal conjunctivitis, or after the prolonged use of atropin on a susceptible conjunctiva, the epithelial layer of the entire tarsal conjunctiva, and that of the cul-de-sacs as well, will be thrown up into folds containing a vascular areolar tissue infiltrated with leukocytes; these folds are called granulations (see Fig. 397, *b*). The epithelium may consist of its normal two layers and not be much altered, or it may be considerably thickened, the columnar cells of the superficial layer being elongated and pointed, and increased in number until the layer may be several cells deep. When examined clinically, the conjunctiva appears soft and velvety and of a bright-red color. This simple papillary conjunctivitis may undergo complete resolution.

A particular variety of papillary conjunctivitis is that known as the horny granulations of vernal catarrh, which are papillary formations, often large and irregular in shape, composed of dense fibrous tissue partially degenerated and of almost cartilaginous hardness, with but few blood-vessels. Clinically these granulations appear as pale elevated nodules, sometimes pedunculated, having a smooth and glassy surface, due to a thin membranous coating of fibrin.

Follicular Conjunctivitis.—This is a disease of poorly nourished children dwelling amid unhygienic surroundings; it is common in schools and asylums. The epithelium is not much altered, nor is the conjunctiva diffusely infiltrated, but nodular accumulations of leukocytes forming lymph-follicles are scattered through the adenoid tissue of the palpebral and retrotarsal conjunctiva. Communicating with these lymph-follicles are dilated lymph-vessels, and the follicles are, so to speak, small lymph-glands. When examined clinically, the conjunctiva does not appear much inflamed, but a number of gelatinous globules are seen arranged irregularly or in rows just beneath the epithelium. The leukocytes composing these follicles may be absorbed, leaving the conjunctiva again normal.

Trachoma.—This is usually a combination of the two forms of con-

conjunctival affection just described, and the conjunctiva, when once attacked with trachoma, does not return to its former normal state.

The earlier stages of trachoma can be studied best in the cul-de-sacs. Here will be found broad papillary elevations with an occasional Henle's gland between them (Fig. 395). The epithelium in most places consists of several layers and contains numbers of goblet-cells. Scattered here and there near the surface of the larger papillæ are follicles composed of densely packed leukocytes with numbers of large phagocytic cells among them. Beneath the follicles are dilated lymph-vessels filled with leukocytes, and scattered about the follicles and extending into their interiors are numerous blood-vessels. The lymphadenoid tissue between the follicles is diffusely infiltrated with leukocytes, particularly near the surface, and the follicle sometimes passes over, without a sharp line of demarcation, into the diffuse infiltration of the neighborhood; but usually there are a few fibers about the follicle which form a delicate capsule. The epithelium directly over the follicles is thin, irregular, and pavement-like. As the disease progresses the adenoid tissue grows more fibrous and shrinks, compressing the follicles,

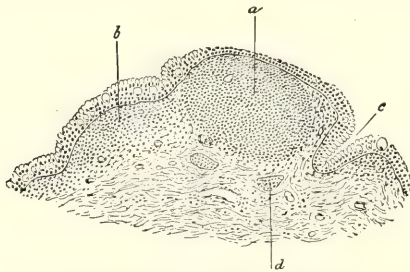


FIG. 395.—Trachoma of the retrotarsal fold: *a*, follicle; *b*, diffuse infiltration; *c*, Henle's gland with goblet-cells; *d*, lymph-vessel filled with leukocytes. $\times 30$.

which then, as a rule, burst through the thinned epithelium and discharge on the surface of the conjunctiva. The cavities so left fill with connective tissue and cicatrize. With the further shrinking thus brought about, the cul-de-sacs are rendered shallow and the tarsus is curved inward, causing entropion.

The causes of follicular conjunctivitis and of trachoma are, notwithstanding much investigation, still unknown, and it is not even ascertained whether or not either is really due to a specific micro-organism. No micro-organisms have been discovered in the tissues themselves, and, of the many found in the secretion, none has produced typical trachoma when inoculated. They that have studied trachoma in Egypt have come to look upon it there as a chronic sequel of the acute epidemic ophthalmia which prevails at certain seasons of the year, and is caused sometimes by the Weeks bacillus and oftener by the gonococcus.

Tuberculosis.—Tuberculosis may appear in the conjunctiva in the form of a primary ulcer caused by infection after injury or operation, or by the bacilli gaining entrance to a gland. Lupus also is seen at times, having spread to the conjunctiva from the skin or having passed through the

lacrimal duct from the nose. The clinical diagnosis of primary tuberculous ulcer is often extremely difficult in the beginning, and the most reliable test is to introduce a particle of the suspected tissue into the anterior chamber of a rabbit, when, if the tissue be tuberculous, a nodular iritis will make its appearance in about four weeks.

A peculiar nodular so-called pseudo-tuberculous inflammation with giant cells is brought about by the penetration into the conjunctiva of the hairs of certain varieties of caterpillar. These hairs may, if the cornea is perforated, cause a like nodular inflammation in the iris.

Syphilis and Lepra.—Chancre is seen occasionally on the lid-margin. Lepra-nodules also may develop here.

Pemphigus.—Pemphigus of the conjunctiva may occur with, or even precede, pemphigus of the skin. It commences by the development of vesicles which quickly give place to ulcers leading to the formation of scars, and bringing about a condition of essential shrinking of the conjunctiva with incurable symblepharon, followed by ulceration of the cornea.

Pinguecula.—Pinguecula is a yellowish elevation appearing in the conjunctiva of middle-aged persons, situated near the nasal margin of the cornea or more rarely near the temporal margin. Two forms are distin-

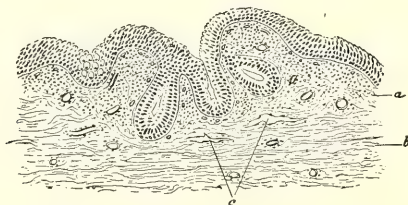


FIG. 396.—Pterygium: *a*, adenoid layer; *b*, tense fibrous layer; *c*, lymph-vessels.

guished: a scleral and a conjunctival form, but mixed forms are not infrequent. The epithelium dips in, forming glands and cysts; the connective tissue is hypertrophied and contains hyaline deposits; and there is a marked increase in the number of elastic fibers.

This formation is thought by some to be the forerunner of pterygium, which is a growth of conjunctival tissue over the cornea, with peculiar changes in both epithelium and connective tissue (Fig. 396). The epithelium of pterygium is for the most part a modified conjunctival epithelium thrown into folds which, in transverse section, resemble the folds of papillary conjunctivitis. Just beneath the epithelium is a lymphadenoid tissue with many small vessels. Deeper, replacing Bowman's membrane, is a loose tissue composed of fibrillæ, tense and stretched in the direction of the center of the cornea. Among the fibrillæ are large blood- and lymph-vessels also extending toward the center of the cornea. The overlying epithelium consists of a basal layer of cuboidal cells, and, above this, of one or more layers of cylindric or pointed cells. These latter cells at any given point run parallel to one another, but rarely quite perpendicular to the surface. In the shallower depressions are many goblet-cells, and the deeper depressions lead to the formation of glands and cysts.

Conjunctival tissue growing into a marginal defect in the cornea leads to a condition known as pseudo-pterygium.

Cysts.—Cysts may arise in the conjunctiva from the dilatation of lymph-vessels or from the occlusion of any of the glands. Since most cysts are small and lined with but a single layer of endothelium, it is probable that they represent dilated lymph-vessels.

Hordeolum and **chalazion** are the results respectively of acute and chronic inflammation in and about the Meibomian glands.

After the acini of a Meibomian gland have been infected by micro-organisms passing in through the duct which opens on the lid-margin, there may be set up an acute suppurative inflammation—hordeolum, similar to that of the glands about the eyelashes—or there may be brought about a chronic proliferative inflammation—chalazion. Chalazion is a mass of granulation-cells, including some giant cells, enclosed in a fibrous capsule (Fig. 397). In its growth it destroys the tarsus over a certain area, and finally perforates both tarsus and conjunctiva and is extruded on the conjunctival surface. If of long standing, the center of the mass may break down into a puriform material, or the entire contents may become liquefied, forming a cyst with a fibrous capsule. Accompanying this swelling there will often be a papillary conjunctivitis. Occasionally a beginning tuberculosis or epithelioma may simulate a simple chalazion which has opened spontaneously.

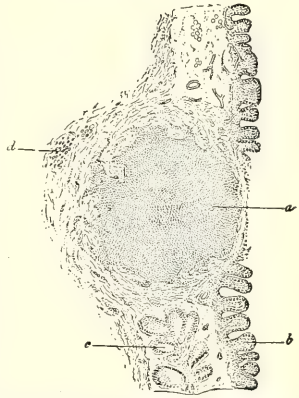


FIG. 397.—Chalazion: a, granulation-tissue of the chalazion; b, papillary conjunctivitis; c, Meibomian gland; d, fibers of the orbicularis muscle. $\times 12$. (Preparation by A. H. Knapp.)

Tumors. — Fibroma. — Polypoid growths are occasionally seen, arising by a pedicle from the conjunctiva of the

lid or cul-de-sac, and are either granulomas or fibromas. Granuloma is covered with a thin layer of epithelium, and is composed of granulation-tissue, supplied in many cases with a very close network of thin-walled vessels which are readily ruptured. When rupture of these occurs, the entire tumor may have a blood-stained appearance or there may be a discharge of blood from the conjunctiva. Hence the expressions “bloody tears” and “bleeding polypi.” Fibroma is composed of dense connective tissue, and contains few vessels. It is frequently flattened and its surface may even be hollowed out by its pressure against the ball, so that it comes to be more or less cup-shaped. The smaller polypi are apt to be cellular and the larger ones fibrous, while mixed forms are not infrequent.

Papilloma of the conjunctiva of the lids or cul-de-sacs is an extremely rare tumor. It is composed of a vascular, fibrous pedicle or base from which spring tufts of long, slender, papillary projections branching near the ends and covered each with a sheath of epithelium, so thick relatively that the connective-tissue axis of the papilla appears insignificant. The axial portion of each papilla is fibrous at its base, but toward its narrow termina-

tion it becomes more cellular and is infiltrated with leukocytes. The epithelium consists of cuboidal, cylindric, or spindle-cells arranged radially in a layer from six to a dozen or more cells deep. The superficial stratum usually consists of flattened cells, but in a case described by Wagenmann it was composed of goblet-cells exclusively. Goblet-cells are found in all conjunctival growths as well as in the normal conjunctiva, but they lie most frequently in the deeper layers, and this arrangement described by Wagenmann is unique.

Papilloma more frequently develop at the sclerocorneal junctions, and occasionally involves the cornea. In the latter case it is frequently questionable whether the growth is not a true epithelioma. Weeks, however, described a case of undoubted papilloma beginning in the conjunctiva and spreading over the entire cornea. In his case the growth lay anterior to Bowman's membrane, which was not much affected. Malignant growths invading the cornea pass, as a rule, beneath Bowman's membrane or destroy it at once.

Osteoma has been seen a few times lying beneath the conjunctiva, between the insertions of the superior and external rectus.

Lipoma is the commonest of the congenital tumors of the ball, appear-

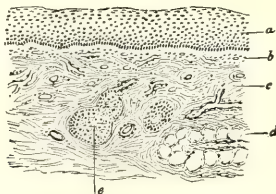


FIG. 398.—Dermoid tumor: a, epithelial layer; b, thin adenoid layer; c, dense connective-tissue bundles; d, fatty tissue; e, gland.

ing as a wedge-shaped mass near the equator of the eye, between the external and inferior rectus. It is composed of fibrous and fatty tissue covered with a thickened conjunctiva, and probably originates as a hernia of the orbital fat.

Dermoid Cysts.—The dermoid is a congenital tumor resting as a hemispherical mass half on the sclera and half on the cornea at the infero-temporal margin. It is dense and opaque, of a milky or yellowish color, and it has a smooth surface, occasionally presenting hairs. The epithelium covering it is thick, smooth, and regular, resembling that of the cornea (Fig. 398).

Beneath the epithelium is a very thin lymphadenoid layer, while the bulk of the tumor consists of dense interlacing fiber-bundles with undulating vessels among them, and glands, hair-follicles, and fatty tissue as in the normal skin.

Sarcoma and Carcinoma.—Malignant tumors may be primary in the conjunctiva, but more frequently they are due to the extension of growths beginning on the lids or in the orbit. Sarcoma may develop from a pigment-spot anywhere in the bulbar conjunctiva. The tumor is then likely to be pedunculated, the pedicle consisting of connective tissue and the sclera not

being involved. Such tumors can readily be peeled off from the sclera and do not return. Sarcoma more frequently develops at the limbus and then, usually, like epithelioma developing primarily at this point, it forms a flatter tumor, which involves the sclera and has a tendency to invade the cornea. The complete removal of such tumors is difficult. Finally, sarcoma originating in the orbit may spread forward along the sclera, or epithelioma of the lid may spread along the conjunctiva of the cul-de-sac and thus reach the sclera. Such tumors are preceded in their extension by a zone of leukocytic infiltration. They spread along in the episcleral tissue and the superficial layers of the sclera until they reach the sclerocorneal junction, where they may follow the perforating vessels and form nodules deep in the sclera, or even, in rare instances, spread to the uveal tract. The conjunctival epithelium is raised, and as the cornea is reached the corneal epithelium with Bowman's membrane is raised and the tumor invades the superficial layers of the cornea and destroys them.

Sarcoma of the conjunctiva is usually pigmented and very vascular; carcinoma is, in the majority of cases, unpigmented. Carcinoma is prone to ulceration, but sarcoma usually remains covered with an unbroken layer of epithelium. This covering layer of epithelium may, as in the case of pigmented sarcoma of the skin, contain pigment. Such a sarcoma recently examined by the writer grew on a conjunctiva from which a similar tumor had been removed seventeen years before, and, teased preparations then showing pigmented epithelium, it was reported as a case of melanotic epithelioma. The histology of these tumors of the limbus is such that their classification is difficult, and in the literature much confusion exists not only as respects the confounding of papilloma and carcinoma, but even in distinguishing between sarcoma and carcinoma.

THE CORNEA.

The cornea, because of its exposed position and the delicacy of its protecting epithelium, is particularly subject to infection by micro-organisms from without, which set up a suppurative inflammation in its superficial lamellæ. And, since the cornea obtains its nutriment only partially from the vessels of the conjunctiva, and more particularly from the vessels of the sclera and ciliary body, it takes part, in its deeper lamellæ, in many of the scleral and uveal inflammations that arise from endogenous infection, in which micro-organisms or toxic substances are carried to these parts through the circulation. Furthermore, the cornea is subject to invasion from the extension of most of the neoplasms that originate in neighboring parts.

SUPPURATIVE INFLAMMATIONS.

Infiltration of the Cornea.—A certain number of leukocytes are normally present in the lymph-spaces of the cornea, and in simple infiltration this physiologic condition is merely exaggerated. The interlamellar spaces of a limited area of the cornea are distended with quantities of closely packed leukocytes, gradually becoming less numerous at the margins of the infiltration, but continuing, in small groups or singly, even to the corneal margin, from the blood-vessels of which they have originally wandered (Fig. 399). The liquid in the lymph-spaces is increased in quantity and altered in quality, precipitating fibrin. If the infiltration is in the super-

ficial lamellæ, the surface of the cornea will appear stippled and its natural luster will be lost, owing to the swelling and separation of the epithelial cells, which render the surface uneven. At this stage the infiltration may still undergo resolution, since those leukocytes which preserve their vitality may wander or be carried back to the vessels, while the dead leukocytes and fibrin may break down and be absorbed. If this takes place, the

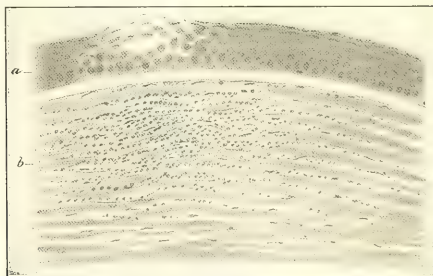


FIG. 399.—Infiltration of the cornea: a, loosened epithelium; b, leukocytes between the lamellæ (adapted).

cornea regains its transparency and returns to its normal state, but if the process is progressive, the infiltration passes over into ulceration.

Ulcer of the Cornea.—The first stage of actual ulceration is the softening of the corneal lamellæ and the entrance into their substance of the leukocytes which in the earlier stage of infiltration were confined entirely to the lymph-spaces (Fig. 400). The leukocytes lose their vitality, and the corneal epithelium is cast off in strips. The superficial lamellæ become necrotic, and so does the membrane of Bowman, which offers little resistance to inflammatory processes, and a swollen necrotic mass of corneal tissue filled

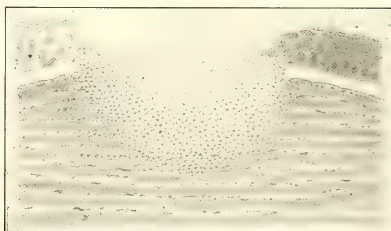


FIG. 400.—Ulcer of the cornea (adapted).

with pus-cells projects above the normal surface of the cornea and is progressively cast off. This *progressive* stage may continue, the purulent infiltration and necrosis extending; or the leukocytes at the margin of the ulcer may form a line of demarcation, after which the central mass sloughs off, leaving a clean base composed of the swollen ends of the lamellæ, and the ulcer is said to be in the *reparative* stage.

The corneal elements have, so far, played merely a passive rôle in the ulceration, but they now take an active part in the repair. Blood-vessels push in toward the ulcer from the periphery of the cornea; the corneal corpuscles at the margin of the defect proliferate and form new connective-tissue cells; and the corneal epithelium pushes in, in a thin layer, on all sides from the margins of the defect, finally covering its base with a thick, smooth layer, and



FIG. 401.—Ulcer cavity covered with a uniform layer of epithelium: *a*, proliferating corneal corpuscles; *b*, new blood-vessel (adapted).

restoring the normal luster of the surface (Fig. 401). Under the protecting epithelium the new formative cells become spindle-shaped and then produce fibers; and, this process continuing from below, the new vascular fibrous tissue fills the defect and pushes the epithelium outward until the normal curvature of the cornea is more or less perfectly restored (Fig. 402). Since the membrane of Bowman is never reproduced, the lower surface of the

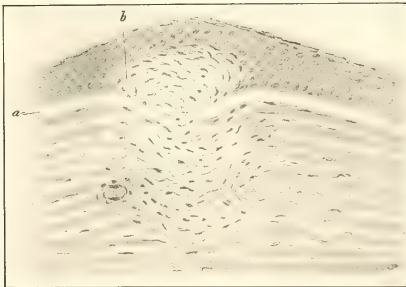


FIG. 402.—Scar in the cornea after a perforating wound: *a*, Bowman's membrane; *b*, scar-tissue between Bowman's membrane and epithelium. $\times 100$.

epithelial layer, lacking the even support of a basement membrane, remains irregular. And the ends of Bowman's membrane being sometimes drawn backward by the scar, the new fibrous tissue may push in for a distance between Bowman's membrane and the epithelium. In the course of time the blood-vessels of the scar disappear, the nuclei become fewer, and the fibers assume a more regular, laminated arrangement, rendering the scar less opaque.

More destructive than this ordinary mild type of ulcer, with a tendency to heal spontaneously, is the type now to be described.

Serpent Ulcer of the Cornea, or Hypopyon Keratitis.—

Serpent ulcer, instead of clearing and undergoing cicatrization like the milder type of ulcer, spreads laterally and increases slowly in depth, ultimately leading to perforation of the cornea; and even from its commencement it excites visible inflammatory changes in the interior of the eye.

At first the aqueous humor grows turbid from the presence of leukocytes and fibrin, and soon liquid pus, containing some iris-pigment, appears at the bottom of the anterior chamber (Fig. 403). The vessels about the corneal margin are congested, and the tissues about them are infiltrated with leukocytes. The ligamentum pectinatum is also densely infiltrated with leukocytes, and the infiltration continues among the posterior lamellæ of the cornea. The endothelium of the iris is cast off, and on the anterior surface of both iris and lens a fibrinous exudation appears, with many leukocytes entan-

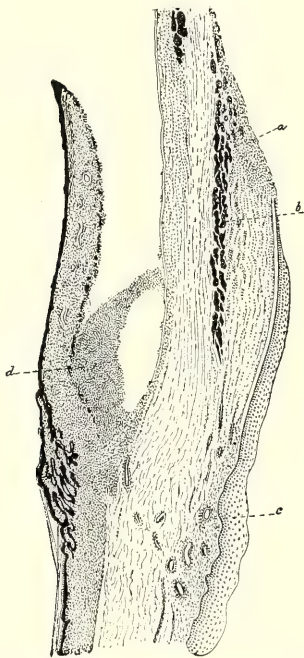


FIG. 403.—Serpent ulcer of the cornea: *a*, inferior margin of the ulcer; *b*, colonies of pneumococci; *c*, episcleral vessels; *d*, hypopyon. The endothelium is cast off entirely; the ligamentum pectinatum, iris, and ciliary body are densely infiltrated with leukocytes. $\times 25$.

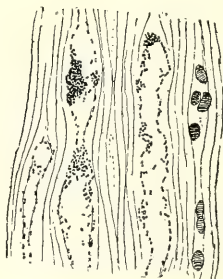


FIG. 404.—Pneumococci spreading along the interlamellar lymph-spaces of the cornea. $\times 500$.

gled in it. Leukocytes are also present in considerable number on and among the endothelial cells lining the membrane of Descemet. In cases of virulent infection the endothelium behind the ulcer is cast off, and a fibrinous coagulum may be deposited on the bare membrane of Descemet. This gives rise to a clinical picture which is often wrongly interpreted as representing the passage of pus through the cornea and its flowing down to the bottom of the anterior chamber. The exudation at the bottom of the chamber does not contain much fibrin, and usually consists of liquid pus.

The ulcer itself exhibits a purulent infiltration at its edges, and spreads laterally with an overhanging margin; but the infiltration may occupy one edge only, while at the opposite edge new vessels are appearing and the reparative process is under way. Foci of purulent infiltration appear here and there in the floor of the ulcer and it grows deeper, the corneal lamellæ sloughing away, one after another, until the membrane of Descemet is exposed. When masses of leukocytes lie on its posterior surface the membrane of Descemet may break down early; but it often happens that it is not immediately perforated, and it then bulges forward and appears as a transparent bead in the floor of the ulcer. Ultimately it ruptures, permitting the escape of the aqueous humor and the collapse of the anterior chamber, and at times the escape of the lens. After perforation takes place the infection may be carried deeper into the eye and cause panophthalmitis, or, as is more frequently the case, the destructive inflammation may cease and the corneal wound heal.

The membrane of Descemet, unlike the membrane of Bowman, is most resistant to inflammatory processes. It ruptures under pressure, but it is rarely destroyed; and after corneal ulceration it remains, wrinkled up, in the eye. Since it is a cuticular secretion of the endothelial cells, these cells, if detached from the membrane by the growth of new tissue between them, may secrete a new membrane in the new position, just as the capsular epithelium of the lens, if separated from the capsule, may secrete a new capsule.

The healing process after perforation from an ulcer or wound differs according to the location and size of the perforation. If the perforation is small and in the pupillary area, the corneal epithelium dips down into it, while the corneal corpuscles proliferate and form scar-tissue, which closes the defect. The ends of the membrane of Descemet are drawn up into the scar, and a permanent depression remains in the posterior surface of the cornea. The closure of the defect may not be perfect, however, and in that case a fistula remains. If the perforation is large or not in the pupillary area, the iris falls forward and blocks it, more or less completely, and then takes an active part in the production of the scar, to which it remains attached (adherent leukoma). When there is actual prolapse of the iris, the protruding portion, if constricted, soon sloughs off, while the incarcerated portion heals into the scar. But if there is a large defect in the cornea and a broad prolapse of iris, the latter will throw out new connective tissue on its surface, and this will be covered with corneal epithelium growing over it from the sides; and with the subsequent contraction there will be produced a flat or a bulging scar, in the formation of which the cornea has furnished only the epithelium. An excessive formation of granulation-tissue from the iris at times gives rise to a projecting swelling known as granuloma of the iris.

When a considerable area of the cornea has been replaced by iris and scar-tissue, the adherent leukoma thus formed is likely, sooner or later, to yield to the intra-ocular pressure and bulge forward, forming what is called a staphyloma. Staphyloma may be partial or total, and it may be of various forms. Frequently it is conical (Fig. 405); or, if a greater portion of the iris is involved, the scar may bulge not only anteriorly, but also laterally, thus stretching or rupturing the suspensory ligament of the lens. Staphyloma of the cornea usually leads later to secondary glaucoma, and with the increased tension the cornea bulges still more, and the sclera becomes ectatic,

so that the size of the eye is greatly increased, and the outer coat, becoming progressively weaker, may finally burst and allow the escape of some of the ocular contents. In other cases, when most of the cornea has been destroyed, the resulting scar, instead of bulging, shrinks and becomes flat—a condition which is called anterior phthisis.

We owe chiefly to Leber our present exact knowledge of the process of corneal suppuration—in previous times a subject of interminable discussion—and the incontestably correct ideas which he enunciated a number of years ago have now gained general acceptance.

Violent corneal inflammation may be caused by various sorts of aspergillus and by the *Leptothrix buccalis*; inflammations of varying intensity may be due to the staphylococci, the streptococcus, and some pyogenic bacilli; and the typical serpent ulcer is usually produced by the pneumococcus.

The infecting micro-organisms enter through a defect in the corneal

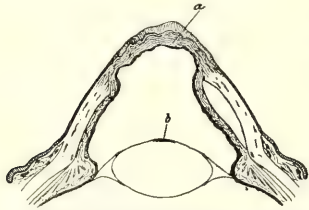


FIG. 405.—Conical staphyloma of the cornea following perforation of central ulcer: a, scar with thickened epithelium; b, anterior polar cataract. $\times 3$.

epithelium, but they are not necessarily brought in at the time of injury, and they more frequently enter later from the conjunctival sac, in which pathogenic micro-organisms are often present. Clinically it is noticed that the cases of severe infection frequently occur in patients with chronic dacryocystitis, the mucopurulent discharge in this affection usually containing the pneumococcus. The pneumococcus when it gains entrance to the cornea proliferates and spreads laterally along the lymph-spaces, gradually forming large colonies (Figs. 403 and 404). These colonies extend under the margins of the ulcer, and thus is explained the tendency of the ulcer to spread laterally with undermined edges.

The process following inoculation is easily studied in experimental ulcers in animals. When a considerable quantity of a culture of virulent staphylococcus is introduced into the cornea, the developing colonies give rise to soluble toxins, which are diffused through the cornea and into neighboring vascular parts. These toxins exercise on leukocytes positive chemotaxis, and the leukocytes emerge from the vessels and, by ameboid movements, rapidly wander in the direction of the greater concentration of the toxins, *i. e.*, toward the infecting colony. When the inoculation is not made in the center of the cornea, the leukocytes wander in mostly from the conjunctival and episcleral vessels of the adjoining portion of the corneal margin; but when the inoculation is made near the center of the cornea, the leukocytes wander in from all sides, and a considerable number come from the deeper scleral and uveal vessels, and it is found then that uveal inflammatory complications and hypopyon are more frequent. The leukocytes, after entering the cornea, wander to the point of inoculation and there succumb to the higher concentration of the toxins, losing their power of mobility. In cases of virulent infection the leukocytes lose their vitality some distance away, and in experimental ulcers there will sometimes be found about the focus of infection a necrotic but uninfiltated zone of corneal tissue, surrounded at a little distance by a zone of dense infiltration. The toxins themselves may

cause necrosis of the corneal lamellæ, and it is thought also that the dead leukocytes furnish a proteolytic ferment. The necrotic mass containing the micro-organisms sloughs off, and with the expulsion of the micro-organisms the reparative process begins.

It was long contended, erroneously, that the corneal corpuscles proliferate to form the pus-cells, but it is now recognized that although the corneal corpuscles about an ulcer may proliferate to some extent before becoming necrotic, the new cells thus produced are but few as compared with the immigrated leukocytes. Another bitterly disputed point was in regard to the source of the pus in the hypopyon, the old idea being that it came from the corneal ulcer. But pus appears in the anterior chamber at a time when the infiltration is confined to the surface of the cornea; and not only has it been shown that the leukocytes never wander away from a progressive ulcer, but it is known that leukocytes from the conjunctival sac pass into the ulcer. The pus in the anterior chamber is not infectious, and it is composed of leukocytes which have been thrown out from the surface of the iris or through the ligamentum pectinatum. The leukocytes which gain a foothold on the posterior surface of the cornea wander toward the ulcer along the endothelium or in the deposits of fibrin, while others which float free in the aqueous humor gravitate down to the bottom of the anterior chamber, whence they quickly disappear when the source of infection is removed. It is now generally recognized that a stage of corneal abscess, which was formerly described as following the stage of infiltration and preceding the stage of ulceration, does not really exist, although some clinicians still use the term abscess to describe the ulcer in hypopyon keratitis.

Other Suppurative Affections.—**Keratomalacia** is a rapid sloughing of the cornea which occurs in poorly nourished infants suffering from fevers or intestinal disorders. The disease, as a rule, begins with xerosis of the conjunctiva and margin of the cornea, which is a process of fatty changes and sloughing of the epithelium, rendering it rough and dry, and giving it the appearance of having been smeared with tallow. The xerosis permits ectogenous infection of the cornea, a rapidly spreading ulcer appears, and the entire cornea melts away.

Phlyctenulæ of the cornea, fornix, or conjunctiva begin as small localized accumulations of leukocytes just beneath the epithelium. The epithelium is cast off in a few hours, leaving a small ulcer which may quickly heal or which may undergo subsequent infection and spread. The children in whom phlyctenulæ repeatedly occur have, as a rule, adenoid vegetations in the pharynx, a discharge from the nose, eczema and pustules of the face, and enlargement of the lymphatic glands of the head and neck.

NONSUPPURATIVE AFFECTIONS OF THE CORNEA.

These are characterized in general by infiltration of the parenchyma of the cornea with leukocytes, by loosening and slight structural changes in the lamellæ, by the deposition of fibrin, which, if not absorbed, may be organized into connective tissue or remain as hyaline matter, and by the extension into the cornea of new-formed blood-vessels.

Superficial Inflammations.—**Pannus** is caused by recurrent phlyctenular inflammation, by the scratching of inverted eyelashes, and principally by the rubbing of the rough upper lid in the cicatricial stage of

trachoma. In its production a conjunctival and episcleral infiltration at the margin of the cornea elevates the marginal epithelium and allows leukocytes and new-formed blood-vessels to pass in between the epithelium and Bowman's membrane. The leukocytes and new vessels may soon be absorbed and disappear or the process may continue, when Bowman's membrane will ultimately be destroyed, and a thin layer of new connective tissue will be formed between the epithelium and the parenchyma of the cornea, causing a permanent opacity.

Vesicles are formed by the elevation of the corneal epithelium, and in the case of larger bullæ by an elevation of the superficial lamellæ also.

Filamentous keratitis is due to localized disturbances in the corneal epithelium caused by injury or inflammation. Fine filaments are found lying on the cornea, firmly adherent at one end to its surface. In the production of this condition the disturbed epithelial cells grow large and assume unusual shapes, and by the increased proliferation are forced up from the surface while still remaining adherent to the cells below. From the traction and torsion exercised upon these cells by the movements of the lids in winking they are drawn out into long fusiform cells, which are twisted together like the strands in a rope. Each filament comes to consist finally of a cone-shaped base adherent to the cornea and passing over into a thin thread composed of fusiform cells unravelled out at its free end. Only near the base are the individual cells recognizable and the nuclei distinct.

Deep Inflammations.—Parenchymatous keratitis in its typical form, affecting one eye after the other and running a course lasting months, and finally leaving opacities that are more or less permanent, is, as Hutchinson first stated, in nearly every case due to hereditary syphilis. Other forms of deep keratitis more or less similar to this, but not running a typical course, are due to acquired syphilis, tuberculosis, malaria, diabetes, rheumatism, influenza, and other diseases. Most cases of chronic inflammation in the deep lamellæ of the cornea are associated with, and probably dependent upon, inflammation of the uveal tract due to systemic causes. The three chief characteristics are an extension into the cornea of new-formed vessels from the deep vessels in the sclera just before they enter the ciliary body, an infiltration of the posterior lamellæ of the cornea with leukocytes coming from the infiltrated ligamentum pectinatum, and a deposition of cells on the posterior corneal surface. Eyes with true parenchymatous keratitis are rarely obtained for microscopic examination, but a considerable number of eyes enucleated for tuberculosis of the uveal tract are found to exhibit the changes of parenchymatous keratitis, and in some eyes of this sort, the tuberculosis of the iris being masked by the opacity of the cornea, the keratitis has been mistaken in life for typical parenchymatous keratitis.

The eye with tuberculosis of the iris and ciliary body, shown in Fig. 413, exhibits the commencement of the process. The anterior lamellæ of the cornea are normal, while the middle and posterior lamellæ contain many new blood-vessels with groups of leukocytes about them, and the vessels which pass through the sclera into the ciliary body are surrounded by masses of leukocytes. The ligamentum pectinatum is crowded with leukocytes and there is also a dense infiltration in the posterior lamellæ, while little groups of cells lie scattered over the endothelium of the posterior surface of the cornea.

Since this case is tuberculous, giant cells are found in the ligamentum pectinatum, and the groups of cells on the posterior surface of the cornea do not all consist of leukocytes, but the larger groups are made up of epithelioid cells with giant cells among them, and represent incipient tubercles. When the tuberculosis spreads through the ligamentum pectinatum into the cornea and extends among the posterior lamellæ toward the center, or when, following the scleral vessels, it perforates the sclerocorneal junction, new blood-vessels appear in great numbers. In the typical non-tuberculous cases the cellular infiltration becomes excessive and leaves permanent changes in and among the lamellæ, and the vessels, after they cease to carry blood, remain as shrunken cords.

Sclerosing keratitis is characterized by the presence of a yellowish marginal opacity of the cornea caused by new deposits of tissue between the deep lamellæ. It usually follows repeated attacks of scleritis and episcleritis, which are associated with subacute iridocyclitis and occur in rheumatic and gouty individuals. These combined corneal, scleral, and uveal affections are known collectively as anterior uveitis.

Keratitis proceeding from the posterior surface of the cornea is the designation given to deep opacities of the cornea which follow removal of the endothelium. One function of the endothelial layer is the regulation of the passage of liquids, and when the endothelium is removed the aqueous humor enters the exposed portion of the cornea and causes a temporary opacity. The endothelium may be rubbed off during the extraction of cataract, or its function may be interfered with by pressure from a tumor of the iris.

Blood-staining of the cornea occasionally follows profuse hemorrhage into the anterior chamber, and the cornea takes on a grayish-yellow, greenish, or reddish hue except in a periphere zone 2 or 3 millimeters broad, which remains untinged and transparent.

The clinical picture often resembles that of a lens dislocated into the anterior chamber, for which it has been mistaken. Since increased tension and pain frequently ensue, many of these eyes have been enucleated, often needlessly, as it has been found that the stain gradually becomes absorbed from the periphery, leaving a round and uniformly opaque plaque in the center of the cornea, which finally disappears entirely. The entire process of recovery required about ten months in a case observed from the beginning by the writer, but a shorter course has been reported by Treacher Collins. The blood is supposed by Collins to enter the cornea as a soluble hemoglobin and there to be deposited in granules of hematoïdin, which can be seen under the microscope.

Striped keratitis is the name applied to the presence of long stripes in the cornea, which were formerly believed to lie in the parenchyma, but which have been found by Hess to be due to a wrinkling of the membrane of Descemet. Thus radiating stripes are often seen about an ulcer when there is prolapse of the membrane of Descemet just before complete perforation of the cornea; vertical stripes are frequently seen for a short time running downward from the corneal wound after cataract extraction; and stripes arranged in geometric figures may follow sudden diminution of intra-ocular tension and may remain permanently.

THE SCLERA.

The inflammations of the sclera are of two varieties: the superficial form, or *episcleritis*, and the deep form, or true *scleritis*. The marked differences between the two varieties, both as regards their clinical aspects and as regards their etiology and pathology, are due principally to differences in blood-supply of the regions affected. The loose episcleral tissue and the superficial lamellæ of the sclera are abundantly supplied with blood-vessels, but the middle and deep lamellæ have no vessels for their own nutrition, the vessels found here being only such as pass through the sclera on their way to the uveal tract; the vessels lie principally in three situations, viz., the sclerocorneal junction, the equator of the ball, and its posterior pole.

Episcleritis, owing to the rich vascular supply of the superficial layers, is often a severe acute independent inflammation; while scleritis is apt to consist only in a chronic infiltration about the vessels passing through the sclera, occurring when the vessels are congested as the result of uveal inflammation. In the episcleral tissue congestion or inflammation of low degree may accompany uveitis or deep keratitis, but ordinary episcleritis more frequently occurs as a primary and uncomplicated affection, and is observed in adults who are rheumatic, gouty, or syphilitic. The blood- and lymph-vessels are dilated, and the tissues are edematous and infiltrated with leukocytes to such a degree that nodules of considerable size are formed, adherent to the sclera, while the conjunctiva is freely movable above them. The disease usually ends in recovery, but it is prone to relapse, and even after recovery it sometimes leaves the sclera thinned so that the uveal pigment shows through.

Scleritis, the deep form, attacks by preference young persons. It is rarely primary, and the milder cases are mostly to be regarded as secondary to uveitis. The tissues are somewhat edematous, and there is an interlamellar infiltration of leukocytes, chiefly about the vessels, producing a diffuse thickening of the sclera rather than a nodular thickening as in episcleritis. Resolution may occur at this stage or the affection may progress. In the latter case the bundles lose their cement substance, and the component fibrillæ are first separated and later disintegrated. Then the infiltration, previously interlamellar, becomes more diffuse, new vessels make their appearance (Fig. 406), and staphyloma is likely to result. In

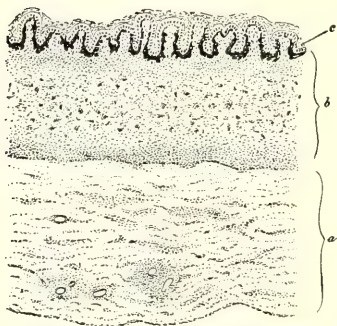


FIG. 406.—Chronic recurrent sclero-uveitis: a, sclera with interlamellar and diffuse infiltration; b, ciliary body in transverse section, infiltrated particularly near its inner and outer margins; c, cyclitic membrane over the ciliary processes. $\times 20$.

other cases, again, there may be proliferation, and new connective tissue is deposited between the lamellæ. Such cases are usually complicated with a sclerosing keratitis.

When there is a chronic inflammation of the uveal tract passing over

into atrophy, the uveal tract, as a rule, acquires adhesion to the sclera in the inflamed region, and thus a chronic infiltration of the sclera is maintained, leading to fibrillar degeneration, followed by thinning and yielding of the sclera with the development of staphyloma. The latter, except in the case of staphyloma posticum, is usually associated with glaucoma.

Scleritis, as said before, occurs, as a rule, in those portions of the sclera through which vessels pass to or from the choroid, viz., the sclerocorneal junction, the equator of the ball, and the posterior pole. Consequently staphyloma occurs in these same regions, and is therefore known, according to its locality, as *intercalary* (between the iris and ciliary body), *ciliary*, *equatorial*, and *posterior*. The anterior staphylomas, and particularly the intercalary, arise through the successive rupture and retraction of the deep lamellæ of the sclera (Fig. 407) rather than from the general thinning occasioned by fibrillar degeneration as in the others.

Thus in secondary glaucoma the periphery of the iris becomes firmly adherent to the cornea, and over the area of adhesion the inner lamellæ of the sclerocorneal junction rupture, and their broken ends are drawn apart,

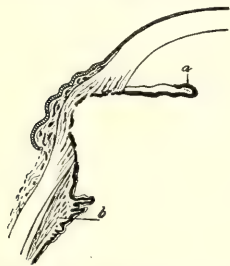


FIG. 407.—Intercalary staphyloma in secondary glaucoma: a, ectropion uveæ; b, flattened ciliary body. $\times 5$.



FIG. 408.—Prolapse of ciliary body through wound of sclera. Episcleral tissue taking part in the formation of the scar. $\times 5$.

increasing the distance between the free portion of the iris and the ciliary body. The superficial lamellæ then bulge under the increased intra-ocular pressure, producing an intercalary staphyloma. Such staphylomas always remain lined with a layer of pigmented tissue representing the remains of the stretched and atrophied peripheric portion of the iris.

Concussion of the eyeball may cause a partial or total detachment of the iris at its ciliary margin; or it may cause a tearing through of the head of the ciliary body, splitting the ciliary muscle into two layers. The iris, which then remains attached to the inner layer, may fall into this cleft and disappear from view in part or wholly. A more severe force will rupture the sclera, usually near the upper corneal margin and in a line concentric with the latter, opening the angle of the anterior chamber. The iris, lens, or vitreous may escape through this rupture and be seen beneath the conjunctiva, which, being elastic, does not often burst. Concussion, if it causes any damage, usually ruptures Schlemm's canal, producing hyphema, and also frequently ruptures the suspensory ligament, permitting the dislocation of the lens; sometimes the capsule of the lens is ruptured near the equator, and a rupture of the choroid not infrequently occurs near the posterior pole of the eye.

When a scleral wound is broad, a knuckle of iris or ciliary body may prolapse into it and heal with a cystoid scar. In the case of smaller wounds the scar-tissue filling the defect comes mostly from the episclera and in lesser degree from the uveal tract, the sclera itself taking very little part in the process (Fig. 408).

In panophthalmitis the perforation is likely to occur in the upper portion of the sclera, just behind the attachment of the rectus muscle, where the sclera is thinnest. When the sclera is attacked the picture of suppurative scleritis is soon followed by rupture, allowing the partial evacuation of the ocular contents, after which phthisis of the globe ensues.

The sclera is very resistant to the extension of **tumors**, and sarcoma or carcinoma may extend from the equator of the ball to the cornea without penetrating deeper than the superficial lamellæ; but when the tumor reaches a perforating vessel or nerve, it may spread along it and even give rise to an intra-ocular tumor.

Syphilitic and tuberculous growths, however, erode the sclera readily. Gumma of the ciliary body develops in the course of iritis, and in debilitated persons it may cause great destruction of tissue, and even perforate the sclera.

The extension of tuberculosis varies with the location of the uveal tuberculosis. The commoner form of tuberculosis of the uveal tract is that in which the iris is filled with tubercles, and tuberculous tissue occupies the surface of the ciliary body without involving the ciliary muscle (Fig. 413). In such cases the sclera or cornea can be affected only after the disease has involved the ligamentum pectinatum. In a rarer form of tuberculosis of the uveal tract the disease begins near or behind the ora serrata and, extending forward, invades the ciliary muscle before involving the surface of the ciliary body. In such cases the sclera becomes irregularly infiltrated with leukocytes and embryonal cells, the latter not always having the characteristic arrangement of tubercle, however, and later, areas of necrosis are seen scattered through the sclera, which are characteristic.

THE UVEAL TRACT.

INFLAMMATIONS OF THE IRIS, CILIARY BODY, AND CHOROID.

The iris and ciliary body, having a common blood-supply, are usually inflamed together, and the inflammations are usually diffuse. The choroid, however, is frequently inflamed alone, and its inflammations are frequently focal. The nontraumatic inflammations of the uveal tract are of endogenous origin, being due to the entrance of toxins or micro-organisms through the medium of the circulation. Toxins alone may apparently give rise to the ordinary acute exudative inflammations, while micro-organisms may give rise also to the acute suppurative inflammation known as metastatic ophthalmia, or to neoplastic inflammations such as lepra and tuberculosis. The traumatic inflammations of the uveal tract follow perforation of the cornea or sclera, and arise from ectogenous infection, a mild infection causing a chronic proliferative inflammation, and a severer infection an acute suppurative inflammation leading to panophthalmitis. Since metastatic ophthalmia in the beginning is usually a retinitis, it will be spoken of in the section devoted to the retina.

Acute Exudative Iridocyclitis.—In the ordinary acute inflam-

mation, due usually to syphilis or rheumatism, the vessels of the iris and ciliary body are congested, the tissues are edematous, and an exudation is thrown out into the aqueous chambers, from both iris and ciliary body. The iris furnishes a fibrinocellular exudation which is deposited in a thick layer on the anterior surface of the iris and the pupillary surface of the lens, and in a thinner layer on the posterior surface of the cornea. The ciliary body, besides secreting an albuminous aqueous humor, throws out a fibrinocellular exudation into the posterior chamber, and also a fibrinous or cellular exudation into the anterior chamber, through the ligamentum pectinatum. Little masses of the cyclitic exudation floating in the anterior chamber become attached to the posterior surface of the cornea low down, and give rise to the clinical picture of punctate keratitis.

Several clinical varieties of iritis are distinguished in accordance with the character of the exudation. When punctate deposits lie on the posterior surface of the cornea, but no fibrinous membranes cloud the pupil, the inflammation is called serous, and is rather a cyclitis than an iritis. When there is a considerable deposition of fibrin on the iris and lens, the inflammation is called plastic, and is rather an iritis than a cyclitis. When the anterior chamber is filled with a mass of fibrin, a condition which is found particularly in gonorrheal and postoperative iritis, the inflammation is called spongy. And, finally, when the exudation is largely cellular and lies at the bottom of the anterior chamber as liquid pus, the inflammation is called purulent; but purulent inflammation, unlike the other forms, is always due to microbial infection.

In the plastic variety of iritis the fibrinous exudation first gums the pupillary margin of the iris to the lens, and then, if the adhesion is not soon broken up, the exudation becomes replaced by connective tissue, and a firm synechia results. When the synechia is circular, including the entire pupillary margin, the newly secreted aqueous humor in the posterior chamber forces the middle zone of the iris forward as a crater-shaped protrusion, giving rise to the condition called *iris bombé*, which is soon followed by glaucoma.

In the ordinary acute iridocyclitis the tissues are not much infiltrated with leukocytes, and, as a rule, there is complete restitution except as regards the synechiae, which may remain. But in the cases in which there is much cellular infiltration the tissues are likely to become atrophic, and there is a disposition to the formation of iridic and cyclitic membranes. The later processes, in cases of this sort, are similar to those occurring in the proliferative inflammation about to be described, which comes on after ectogenous infection.

Iridocyclitis from External Infection.—When the cornea or sclera has been perforated, and pathogenic micro-organisms have been carried into the eye or have wandered in later from the conjunctival sac, the severity of the resulting inflammation depends upon the virulence of the micro-organisms. A mild infection gives rise to a plastic inflammation characterized by the development of new membranes which contract and produce atrophy of the ball, while the connective-tissue cells proliferate and cause sclerosis of the tissues. A more virulent infection gives rise to suppurative inflammation and to the discharge of the contents of the ball, which ultimately shrinks to a phthisical stump.

Chronic Proliferative Iridocyclitis.—The commencement of a

proliferative inflammation a few days after injury of the cornea and lens is shown in Fig. 409. The iridic changes here are most marked at the pupillary margin of the iris, where an adhesion has been formed between iris and lens, with proliferation of the pigment-layer of the iris. The pupil is filled with a membrane continuous with the iris. A layer of epithelioid formative cells surrounds the lens, and a new membrane is forming over the pars ciliaris retinae near the ora serrata. A few scattered cells lie near the surface of the ciliary body, in the vitreous and the posterior chamber; there is also a small collection of leukocytes at the bottom of the anterior chamber; and small deposits of leukocytes and fibrin are scattered over the posterior surface of the cornea. At a later stage of the process delicate vascular membranes are found on both surfaces of the iris, over the entire ciliary body and completely around the lens (Fig. 410). As soon as formed, these membranes

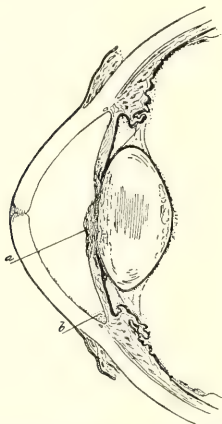


FIG. 409.—Beginning iridocyclitis and traumatic cataract a few days after perforation of cornea and injury of lens: *a*, pupillary membrane; *b*, hypopyon. $\times 4$.

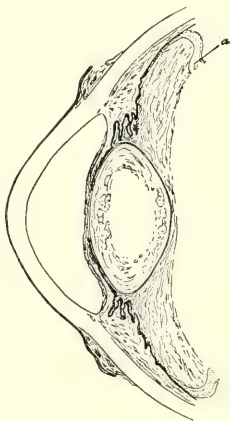


FIG. 410.—Chronic iridocyclitis; new membranes on both surfaces of the iris and about the lens, with beginning cortical cataract: *a*, retina detached at the ora serrata. $\times 4$.

begin to condense and shrink, and the traction which they exert brings about a series of displacements in the eye. First, the ciliary processes are drawn in toward the lens. Then a total posterior synechia is formed and the periphery of the iris is retracted, deepening the periphery of the anterior chamber—a clinical sign of membranous cyclitis. Next, the cyclitic membranes which have extended back to the periphery of the retina detach the retina at the ora serrata.

The lens at this time grows cataractous and its capsule may be wrinkled by the contracting membranes. Later the lens becomes chalky and shrunken, or, if the capsule has been ruptured, new connective tissue may push through the rupture and produce a fibrous cataract, or, the fibers becoming absorbed, there may be left only the wrinkled capsule lined with epithelial cells. As the shrinking of the membranes continues, the retina undergoes a total funnel-shaped detachment, and after this the ciliary body

is detached posteriorly and rotated inward about its fixed point of attachment to the outer coat, the ligamentum pectinatum (Fig. 411). Finally the sclerocorneal junction is drawn in, the pressure of the recti muscles gives a cuboidal shape to the softened globe, and it is said to be atrophied. Recurrent inflammation is now the rule, and sympathetic disturbances in the other eye are likely to arise. Throughout the process the uveal tract is infiltrated with leukocytes, and, in accordance with the rule in chronic infiltrations, there is a proliferation of connective tissue, causing a condensation and shrinking of the part and an obliteration of many of its vessels. The iris, when not adherent to the lens, becomes thinned and shortened, the contraction of the stroma drawing the posterior pigment-layer round the pupillary margin to the anterior surface of the iris, a condition called ectropion uveæ (Fig. 407). The cells of the posterior pigment-layer proliferate, and pigmented cellular processes dip down into the new membrane behind the iris. The superficial portion of the ciliary body and the ciliary processes, composed of loose tissue, become atrophic, while a proliferation of the columnar cells of the pars ciliaris retinae takes place, producing a layer of long spindle-cells, often several cells deep, from which cellular processes pass out into the new membrane. In some cases the pigment-epithelium also proliferates and throws out into the new membrane long tubular processes composed of a single layer of cuboidal pigmented cells arranged about a narrow lumen (Fig. 411). The inner ends of these processes often lack pigment and the cuboidal cells here become spindle-shaped, while the tubules themselves branch and anastomose like capillary blood-vessels. Indeed, Berger has considered all the pigmented tubular processes to be blood-vessels, but Alt and Treacher Collins have regarded them as glandular processes, which those near the ciliary body, at least, certainly are. In old cyclitic membranes it is not unusual to find masses of new-formed bone with Haversian canals and medullary spaces. The choroid, which frequently takes part in the process, is transformed into dense fibrous tissue, and it often gains adhesion to the sclera, the suprachoroidal space being obliterated. The pigment-epithelium lying on the choroid proliferates and gives rise to colloid excrescences (Fig. 416), and true bone may form in the choroid or in new membranes on its surface.

Suppurative Uveitis from External Infection.—After the entrance of virulent micro-organisms through an open wound the infected uveal tissue becomes greatly swollen and engorged with leukocytes, and pus collects in the humors of the eye. Beginning where it may, the process soon spreads to all the vascular parts of the ball, becoming a panophthalmitis. The tissues break down, and later are more or less unrecognizable; the pus is discharged through the wound or through a fresh perforation of the sclera;

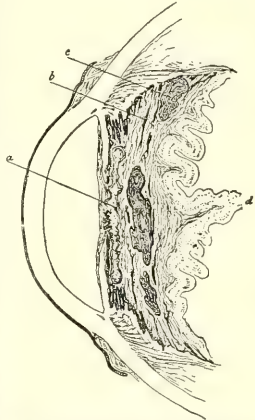


FIG. 411.—Old iridocyclitis after perforation of cornea and penetration of lens: *a*, wrinkled empty lens-capsule; *b*, tubules of pigment-epithelium; *c*, focus of true bone; *d*, retina detached in funnel-shape. $\times 4$.

and the globe shrinks to a stump, which remains free from irritation and does not give rise to sympathetic disturbances, a condition known as phthisis bulbi.

Acute Exudative Choroiditis.—In this inflammation a small area of the choroid becomes congested and edematous, and throws out a serous or fibrinocellular exudation. This exudation may lie between the choroid and retina, or the retina may be infiltrated and a fibrinous mass be deposited on its surface, or the exudation may lie free in the vitreous, giving rise to punctate or membranous opacities. The overlying retina is usually swollen and its vessels congested, and hemorrhage is not infrequent. As the edema of the choroid passes off, new connective-tissue fibers appear, and the loose reticular stroma is converted into dense fibrous tissue. The layers of smaller vessels disappear entirely, and even the large vessels become sclerosed and obstructed and shrink to fibrous cords. In the overlying retina the nerve-structures atrophy and the supporting structures become hypertrophied, while the pigment-epithelium breaks down over the focus and proliferates at its margins. The final outcome is an adhesion between the choroid and retina, both of which have undergone a fibrous degeneration and may be represented only by a nonvascular, nonpigmented, transparent scar.

In **disseminated choroiditis** a number of foci may be inflamed at a time and the process is essentially chronic and atrophic. There is at first a focal retinitis of the outer layers, followed by diffuse fibrous degeneration of the retina with inwandering of pigment.

Proliferative Choroiditis.—This affection is, as a rule, one element of a chronic iridocyclochoroiditis, and may follow a spontaneous chronic iridocyclitis or an iridocyclitis from external infection. It is essentially a diffuse form of inflammation, and consists at first of a general infiltration of leukocytes in the inner layers of the choroid, with scattered foci of denser infiltration. Later, sclerosis of the tissues takes place. The pigment-epithelium, which normally secretes the lamina vitrea, undergoes proliferation, and colloid excrescences are deposited on the lamina vitrea, partly due to secretion of the cells, and partly, it may be, to degeneration of the cells themselves. Bone formation also is frequent, and the choroiditis is often associated with a diffuse retinitis of the inner layers or a general fibrous degeneration of the retina with the in-wandering of pigment (Fig. 416).

Sympathetic ophthalmia is an inflammation in one eye following a plastic iridocyclitis in the other. The inflammation of the eye primarily affected is usually traceable to external infection. There are two forms of sympathetic inflammation. The first is a benign neuroretinitis, which is regarded rather as a sign of "irritation," and which never leads directly to uveal inflammation, although it may be followed later by sympathetic iridocyclitis. The second is a proliferative iridocyclitis, with no very acute signs of inflammation, but with a disposition to the formation of new membranes, which proceeds, usually unchecked by treatment, to the complete abolishment of vision. It was thought some years ago that the migratory theory of its origin—*i. e.*, that sympathetic ophthalmia is due to the actual transmission of micro-organisms from one eye to the other along the optic nerves and chiasm, had been proved by Deutschmann's experiments, but his results have now been utterly discredited, and we are thrown back upon the theory that it is due to reflex irritation conveyed along the ciliary nerves, a theory which is even less plausible than the other and has no very convincing arguments to support it.

Infectious Processes.—Condyloma and gumma form either at the pupillary or the ciliary margin of the iris in the course of severe acute iritis.

Tubercles make their appearance as little yellowish, nonvascular nodules, scattered over the irregularly thickened iris, in the course of a mild chronic iritis in children (Fig. 412). The tubercles come to occupy the entire iris and then spread back to the superficial portion of the ciliary body. At a given time all stages of development and degeneration may be found. In acute general tuberculosis miliary tubercles may often be found scattered through the choroid. In other cases there may be conglomerate or solitary tubercle, a mass of tuberculous nature, arising in the choroid and involving the retina and optic nerve and ultimately filling the vitreous chamber. A mild or attenuated form of iris tuberculosis may run a benign course, and even cases in which complete destruction of the eye seemed imminent have sometimes been cured. Hence most surgeons to-day delay enucleation, particularly since some believe that tuberculosis is never primary in the uveal tract. Others, however, when no signs of tuberculosis are to be found elsewhere in the body, enucleate the ball with the idea of preventing further infection.

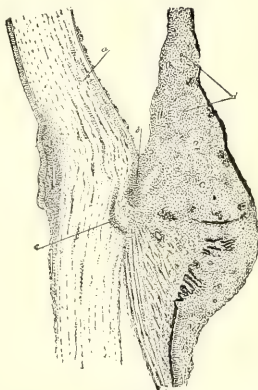


FIG. 412.—Tuberculosis of iris and ciliary body: *a*, cornea with parenchymatous infiltration; *b*, ligamentum pectinatum, infiltrated; *c*, blood-vessel surrounded by infiltration; *d*, tubercles in the iris. $\times 15$.

Lepra-nodules make their appearance in the iris in cases of lepra of the skin.

Lymphomas are occasionally seen in the iris in the form of multiple little grayish-yellow elevations coming on in patients with leukemia. More frequent ocular manifestations of this disease, however, are dense diffuse infiltrations of the episclera, choroid, orbit, and neighboring cavities; and it has repeatedly happened that the surgeon, acting upon a mistaken diagnosis, has removed orbital lymphomas of this sort, instead of treating the general disease.

Tumors.—In the iris are found angioma, melanoma, cystoma, and sarcoma.

Cyst is usually due to the proliferation of epithelial particles that have been carried into the eye by traumatism; and in the rare cases in which its development has not been preceded by perforation of the cornea, it is thought by Schmidt-Rimpler to be due to the closure of one of the crypts on the anterior surface of the iris. These cysts either may be serous, with liquid contents and a lining of epithelium or endothelium, or they may be pearly tumors composed of laminated epithelium which is broken down in the center into an atheromatous mass. Cysts also arise from the splitting apart of the double pigment-layer of the iris and the filling of the cavity with liquid, but cysts of this sort are rarely discovered in life, and occur mostly in eyes with broad posterior synechiæ (Fig. 413).

Primary sarcoma of the iris is very rare. It is almost always pigmented

and is a very vascular tumor, leading to iritis and glaucoma, and it soon perforates the ball. If pigmented, it can be confounded only with melanoma, which is noninflammatory and nonprogressive. Secondary sarcoma at the ciliary margin of the iris, due to extension from the ciliary body, is not infrequent.

In the ciliary body are found cyst, nevus, sarcoma (including myomatous forms), and glandular tumors arising from the pars ciliaris retinae and dipping down into the substance of the ciliary body, which are variously described as adenoma and primary carcinoma. Metastatic carcinoma has



FIG. 413.—Cyst of the entire pigment-layer of the iris, due to membranous iridocyclitis following a perforating injury of the cornea and lens. $\times 4$.

been seen in the ciliary body three or four times, together with metastatic carcinoma in the choroid, of which a score of cases have been observed.

Cyst and nevus occur in the choroid rarely, but sarcoma is relatively common. Sarcoma begins mostly in the middle layers of the choroid, and continues to have a flattened spheroidal or fungus-shape as long as the inner layers of the choroid cover it as a capsule (Fig. 414, 1). But when the lamina vitrea is perforated and the tumor breaks through its choroidal capsule the extracapsular portion grows unrestricted in a spherical form, arising from the flatter portion within the capsule (Fig. 414, 2), or with further growth the entire humor may become spherical (Fig. 414, 3). The retina after a time undergoes a total detachment (Fig. 414, 1), or it remains

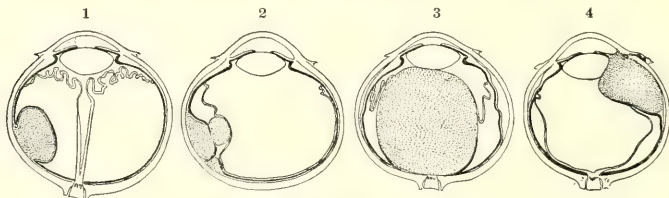


FIG. 414.—Diagrams of sarcoma of the uveal tract.

adherent to the surface of the tumor only, when the latter has perforated its capsule and involved the retina before the general detachment (Fig. 414, 2 and 3).

After detachment of the retina the inflammatory stage comes on, when either glaucoma supervenes or, in exceptional cases, an iridocyclitis is set up, leading to atrophy of the ball. Following the inflammatory stage comes that of local extension. The choroidal tumor now spreads along the optic nerve, ciliary nerves, or the perforating vessels of the sclera, and forms nodules in the orbit, causing exophthalmos. The tumor of the ciliary

body extends into the ciliary margin of the iris and the ligamentum pectinatum, and then follows the anterior ciliary vessels through the sclera and gives rise to epibulbar nodules (Fig. 414, 4). Finally metastases form in other organs.

Sarcoma of the uveal tract is almost always pigmented and is usually a fairly vascular growth, composed of small spindle- or round cells arranged in the ordinary manner. A less common form is an angiosarcoma with vessel-walls consisting only of a single endothelial layer, which is surrounded by a thick sheath of epithelioid cells arranged in concentric layers. And still less common is an alveolar form which has frequently been described as carcinomatous. Occasionally sarcoma may contain cartilaginous or bony islands.

Metastatic carcinoma and the rarer metastatic sarcoma occur in the form of broad, flat tumors near the pole of the eye, extending laterally. The cells are brought in through the posterior ciliary arteries, and may give rise to several foci. In half the cases, too, both eyes are affected.

THE RETINA.

Owing to its composite structure and mixed nutritive supply the retina is the seat of more varied pathologic changes than any other part of the eye. Thus "idiopathic" diffuse retinitis affects chiefly the inner layers which are supplied by the retinal vessels, while the focal inflammations of the choroid have associated with them a retinitis of the outer layers which get their nutritive supply from the choroid. Microbic infections, either ectogenous following injury, or endogenous from metastasis, give rise to suppurative inflammation. And, finally, altered states of the blood or blood-vessels lead to diffuse edema and localized exudations in the different retinal layers. As is the case in the central nervous system, to which the retina is analogous in structure, inflammations and degenerations lead to atrophy of the nerve-elements, while the neuroglia and other supporting elements undergo hyperplasia.

INFLAMMATIONS OF THE RETINA.

Diffuse retinitis is an inflammation often accompanying chronic choroiditis, but not perhaps depending directly upon it. This is the usual syphilitic inflammation. In the beginning the inner, vascular layers of the retina are infiltrated with leukocytes. Later the supporting framework becomes thickened and atrophy of the nerve-fiber and ganglion-cell layers takes place, extending in some cases to the inner nuclear layer. The final outcome may be a condition similar to that observed after embolism of the central artery of the retina, or sometimes in chronic glaucoma, a disappearance of all the nerve-elements supplied by the retinal vessels, while the outer nuclear layer and the rods and cones remain intact (Fig. 415).

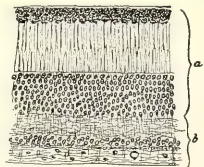


FIG. 415.—Atrophy of the inner layers of the retina from a glaucomatous eye: *a*, perceptible stratum, normal; *b*, conducting stratum with inner nuclear-layer, ganglion cells, and nerve-fibers completely atrophic. The few nuclei here present belong to Müller's fibers or to neuroglia cells. $\times 80$.

Retinitis of the outer layers, on the other hand, depends directly upon choroidal inflammation. In acute disseminate or in acute generalized chorioretinitis the outer layers of the retina become infiltrated and actively take part in the process. In chronic choroiditis the pigment-epithelium proliferates, while the rod-and-cone layer and the outer nuclear layer atrophy. The process may go on until the entire retina comes to be in a state of fibrous degeneration. Colloid excrescences derived from the proliferation of the pigment-epithelium are found scattered through the retina or resting still on the lamina vitrea, and numbers of immigrated pigment-cells lie along

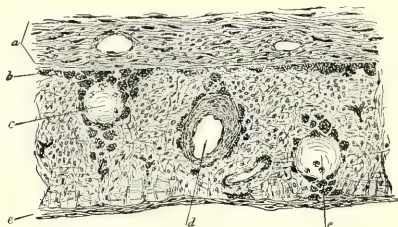


FIG. 416.—Sclerosis of choroid and fibrous degeneration of retina (choroidal form of retinitis pigmentosa): a, choroid; b, pigment-epithelium, atrophic at some points, hypertrophic at others; c, c, colloid excrescences; d, sclerosed blood-vessel; e, fibrous membrane lying on the lamina interna. $\times 80$.

the walls of the sclerosed retinal vessels (Fig. 416). These are the changes found in the retina in typical retinitis pigmentosa also, except that in the uncomplicated form the choroidal changes are limited to sclerosis of the vessels and colloid excrescences do not appear.

Metastatic retinitis (*metastatic ophthalmia*) occurs in puerperal fever, cerebrospinal meningitis, pyemia, and other suppurative affections; the capillaries of the retina and choroid become blocked with micro-organisms that have been taken up into the circulation. The pyemic form of the disease,



FIG. 417.—Puerperal metastatic ophthalmia: a, layer of pigment-epithelium; b, groups of streptococci lying on the pigment-cells; c, streptococci in and among the leukocytes of the subretinal exudation. $\times 500$. (Preparation by Dr. A. B. Kibbe).

most frequently due to puerperal fever, is a severe suppurative inflammation caused by the streptococcus. It is frequently bilateral and usually leads to panophthalmitis. When many of the retinal capillaries are blocked there will appear first the edema and degenerative changes that follow the mechanical interruption of the circulation, and to these will soon be added the infiltration and purulent exudation caused by the toxic products of the streptococcus.

When the emboli are few the streptococci will often be found particularly in groups about the cells of the pigment-epithelium (Fig. 417). There will

first be localized infiltrations of the retina and choroid, with a fibrinopurulent exudation in the aqueous chambers and the anterior portion of the vitreous. Later the retina will become detached and the vitreous will be filled with pus-cells having great numbers of streptococci in and among them. Only in exceptional cases is any vision retained, and this is usually lost later.

A milder form of metastatic ophthalmia, caused by Weichselbaum's *Diplococcus intracellularis meningitidis*, is not infrequent in children, following cerebrospinal meningitis. Usually only one eye is affected. It is still questionable whether the meningococcus may not pass directly from the cranial cavity to the eye as well as be carried in with the blood-current. The inflammation is usually of a proliferative rather than a suppurative character; dull-gray nonvascular membranes cover the fundus, and cyclitic membranes retract the periphery of the iris, establishing a condition frequently mistaken for glioma.

A still milder process, known improperly as retinitis septica, comes on in scurvy and other altered states of the blood, and is characterized by the presence of hemorrhages and white patches in the retina. It is probable that in most cases the retinal changes are merely degenerative, and are due to thrombosis, sclerosis of the retinal vessels, or pathologic conditions of the blood, no micro-organisms being present.

Nephritic Retinitis.—Diseases of the heart and blood-vessels, diabetes, and nephritis all lead to changes in the retina, consisting of swelling of the disk and retina, dilatation and degeneration of the vessels, hemorrhages, and white patches, the ophthalmoscopic picture differing somewhat according to the underlying cause. Nephritic retinitis is the most typical and exhibits all the pathologic changes found in the others, so it alone need be described.

The retinal changes in nephritis may, for convenience of description, be divided into the diffuse, which are common to many retinal affections, and the focal, which are in some measure characteristic of nephritis. The diffuse changes consist of alterations in the vessels, edema of most of the layers of the retina, and hydropic swelling or fatty degeneration of various retinal elements. The vascular changes differ greatly in different cases, but the smaller vessels are usually sclerotic, with proliferation of the endothelium, and in the larger vessels the adventitia is thickened irregularly, often in the form of excrescences; later, calcareous matter may be deposited in the vessel-walls or they may undergo fatty degeneration. In the choroid also the vessel-walls are greatly thickened, chiefly from hypertrophy of the tunica media.

The retinal edema consists in the presence of a clear serum, or a serum mixed with fibrin, in the tissues, separating the various elements (Fig. 419). Thus the nerve-fiber layer is everywhere thickened, and in the periphery of the retina is cystic. The ganglion-cells are surrounded by liquid, so that their outlines are clearly distinguishable, and the cells themselves may be swollen. The inner nuclear layer may be cystic, and the two reticular layers are more coarsely meshed than usual. In the central portion of the retina the nuclei of the outer nuclear layer are pushed outward from the outer reticular layer, so that a narrow zone of rod-and-cone fibers appears

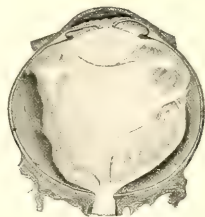


FIG. 418.—Severe, partially purulent metastatic ophthalmia following cerebrospinal meningitis.

between them. And about the macula, where this fiber-zone normally exists, being known as Henle's fiber-layer, great cystic cavities are found, and the enlargement of this layer causes the *limitans externa* to be thrown into folds.

Müller's fibers become swollen and granular. The axones of the nerve-fiber layer undergo varicose hypertrophy, becoming greatly thickened, granular, and irregular in shape. This hydropic swelling is found particularly in the neighborhood of hemorrhages, and when numbers of the fibers are affected,

a white patch remains at the site of the hemorrhage after the blood-elements have been entirely absorbed. The retinal hemorrhages occurring in pernicious anemia lead to this degenerative condition in a high degree, and after death many myelin-like globules are found among the swollen axis-cylinders. The inner segments of the cones are found often to be greatly swollen and granular. This swelling of the rod-and-cone layer, particularly in the neighborhood of the macula, where the cones are most numerous, causes the layer to be detached from the *limitans externa* and to be thrown up into short folds.

About the hemorrhages and elsewhere in the retina may be found numbers of phagocytes, swollen granular leukocytes which have taken up fat-drops formed by the degeneration

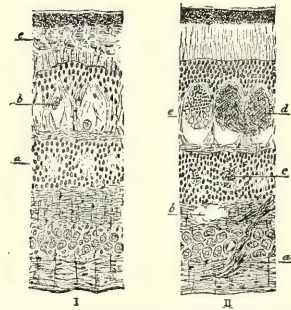


FIG. 419.—Nephritic retinitis near the macula in different eyes: I, showing diffuse changes; II, showing focal exudations. I, *a*, cysts in inner nuclear layer; *b*, cysts in outer nuclear layer, with large fatty cells; *c*, myelin-like degeneration of outer segments of rods and cones, inner segments granular. II, *a*, coarse fibrin; *b*, colloid; *c* and *d*, hemorrhages and fibrin in Henle's fiber-layer and outer nuclear layer; *e*, fatty cells about a hemorrhage. $\times 80$.

of the red blood-corpuscles and of the retinal elements. Besides these nucleated cells there may be found numbers of fatty, granular cells, bodies that have lost all cell-structure, but that probably have had their origin in the fatty infiltration of leukocytes or the fatty changes of nerve-cells.

The choroid also takes part in the nephritic inflammatory process, its vessels being congested and its tissues often infiltrated with leukocytes.

The focal changes, as seen ophthalmoscopically, consist of flame-shaped hemorrhages and large, diffusely outlined, white plaques lying in a zone about the disk, and of smaller, round, sharply outlined hemorrhages and white spots, often confluent, arranged in a radial manner about the macula. The larger hemorrhages are collections in the nerve-fiber layer of red blood-corpuscles which have escaped from the veins and capillaries by diapedesis. The white plaques represent hemorrhages which have undergone resorptive changes, groups of axones which have undergone hydropic swelling, and masses of fibrin, colloid, and hyaline matter. The smaller round white spots about the macula, and in less number about the disk, are due to extravasations from the deeper capillaries into cystic spaces in Henle's layer (Fig. 419, II). In one of these cysts the deposit may consist of fresh red blood-corpuscles; in the next cyst many of the corpuscles may be in a state of disintegration, leukocytes absorbing the fragments; and in the next cyst there may be found only a mass of shrunken fibrin or of colloid matter. The yellow patches of retinitis circinata have recently been found by Amman

to be due to exactly the same retinal conditions. Similar deposits are found also in the smaller cysts of the inner nuclear layer. The optic disk may be swollen and edematous, but there is never much infiltration with leukocytes, either in the disk or retina, and the processes are chiefly of a degenerative character, following nutritive changes and the passive escape from the vessels of different elements of the blood when the vessel-walls are diseased and arterial tension is increased.

Degenerations and Detachment.—Cystic degeneration is a frequent senile change occurring in the periphery of the retina from circulatory disturbances. Cystic cavities arise in the two nuclear layers, and the reticular layer between them eventually being broken down, a single layer of cysts results. A similar process occurring at times at various points in the detached retina leads to the formation of large unilocular cysts of globular form (Fig. 420).

Detachment of the retina may come on spontaneously or be caused by an inflammatory serous exudation from the choroid in nephritis, by a purulent exudation in suppurative choroiditis, by hemorrhage, and by tumor. In the greater number of cases, however, the detachment is of so-called spontaneous origin, and the process, according to the generally accepted Leber-Nordensen theory, is as follows: An inflammation in the choroid leads to fibrillar degeneration of the vitreous. The fibrillæ shrink and detach the vitreous in part, and its liquid constituents, being squeezed out by the shrinking, collect between the vitreous and retina. With the further shrinking of the fibrillæ, particularly near the ora serrata, where they are coarsest, the retina is here drawn inward and ruptured, and the preretinal fluid passes through the rupture and sinks down between the retina and choroid, causing a detachment which descends by gravitation to the bottom of the eye.

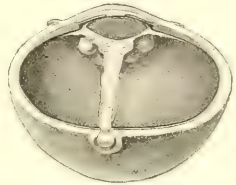


FIG. 420.—Multiple cysts in a detached retina.

Tumors.—**Glioma** of the retina is a disease of fetal life and early childhood; in one-fifth of the cases it affects both eyes. It begins in any of the inner layers of the retina, and may grow either inward, so that nodular masses seem to overlie the retina (glioma endophytum), or it may grow outward so that the retina is apparently detached and elevated (glioma exophytum) (Fig. 421). After a time glaucoma comes on or, more rarely, an iridocyclitis develops, which leads to shrinking of the ball. Following the inflammatory stage the growth perforates the eyeball, passing out through the cornea, or the sclerocorneal junction, or along the optic nerve, or, in rarer cases, extending along the ciliary vessels and nerves. Then the glands of the head are attacked, nodules form on the bones of the skull, and the brain becomes involved. Finally metastases form in distant organs, although, unlike intra-ocular sarcoma, glioma is dangerous rather by reason of its great tendency to



FIG. 421.—Glioma exophytum.

recurrence and to local extension than by a tendency to metastasis. The tumor contains many thick-walled blood-vessels, and about these are sheaths of closely packed small cells having a large nucleus, staining darkly, and very delicate processes. Further from the nutritive supply, the cells are degenerated and do not take the stain. Fatty and calcareous changes are common in the tumor, and the vessel-walls are frequently sclerosed. Glioma of the retina differs from glioma of the central nervous system in being much less fibrillar and in having its cells more closely packed.

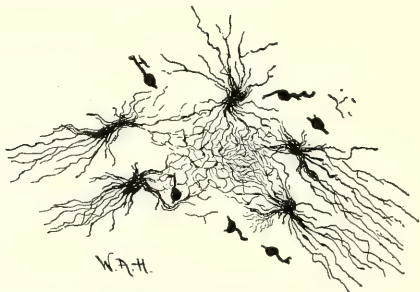


FIG. 422.—Glioma stained by Golgi's method, showing neuroglia-tissue and scattered embryonal nerve-cells. $\times 30$.

Indeed, by some, glioma has been thought to belong in the category of sarcoma, but Golgi's stain shows it to consist of neuroglia-tissue with numbers of small nerve-cells scattered through it (Fig. 422).

In exceptional cases portions of the tumor consist of tubules made up of a layer of long conical cells, each sending a process through an elastic membrane (Fig. 423). This formation is analogous in structure to the cone-nucleus, *limitans externa*, and cone in the normal retina, and has therefore been called neuro-epithelioma of the retina.



FIG. 423.—Tubules of neuro-epithelioma of the retina. $\times 200$.

Clinically glioma presents some difficulties in diagnosis, since several other pathologic conditions may simulate it. These conditions, collectively designated pseudoglioma, are congenital malformations of the anterior portion of the vitreous with remains of the fetal vascular system, conglomerate tubercle, chronic panophthalmitis, and, finally and more frequently, metastatic ophthalmia. Conversely, a uveal inflammation may mask the presence of an existing glioma—a condition recently called cryptoglioma by Schöbl.

THE OPTIC NERVE.

The optic nerve is subject to inflammation of its connective-tissue sheaths and septa, to atrophy of its nerve-fibers, and to tumors.

Inflammations of the Optic Nerve.—The inflammations may be primary or secondary. The primary arise in the course of rheumatism, syphilis, infectious fevers, menstrual disturbances, and various intoxications. The secondary are due to meningitis, sinus-thrombosis, and intracranial tumors, and also to inflammatory exudations and tumors in the orbit. The primary inflammations are mostly cases of *retrobulbar* neuritis, while the secondary are mostly cases of *papillitis* or choked disk.

In the acute cases of retrobulbar neuritis there is inflammatory swelling of the pial sheath and septa (interstitial neuritis), causing compression of the nerve-fibers and decrease in vision. In the chronic cases there is hyperplasia of the septa, causing the same effects. A general diffuse neuritis may lead to total loss of sight, a perineuritis to concentric contraction of the field, an axial neuritis of the papillomacular bundle to central scotoma, and disseminate focal neuritis to small scattered scotomas. In a large percentage of cases, however, retrobulbar neuritis gives rise to central scotoma, at times associated with irregular peripheric contraction of the field. In chronic tobacco amblyopia, with its relative central scotoma, a hyperplasia of the interstitial connective tissue is found just behind the eye, together with atrophy of the nerve-fibers of the papillomacular bundle in its entire course. The initial process here has been thought to be the interstitial retrobulbar neuritis, but this view has been questioned by Nuel, who would place the first changes in the ganglion-cells of the retina, degeneration of which is followed by an ascending atrophy of the nerve-fibers. Retrobulbar neuritis frequently ends in complete recovery, but some cases, particularly those occurring in fevers, exhibit considerable swelling of the disk and quickly go on to atrophy.

Papillitis has been explained in various ways, some regarding it as the result of hydrops of the nerve-sheath, and some as a true infectious inflammation. We know, however, that when the intracranial tension is increased, as in case of tumor, an excess of cerebrospinal fluid is forced into the intervaginal space of the optic nerve. The central retinal artery and vein, which traverse this space to enter the optic nerve a few millimeters behind the ball, are then compressed and an edema of the nerve-head ensues, accompanied with hemorrhages and some exudation of leukocytes. Trephining, and allowing the excess of cerebrospinal fluid to escape, causes a subsidence of the papillitis. In other cases it would appear that there is a true active inflammation of the nerve-head.

Papillitis may pass off, leaving the disk normal, or, in case it continues for a length of time, there is apt to be new formation of connective tissue and peripheric contraction of the field. In acute cases the inflammatory edema compresses the nerve-fibers, while in chronic atrophic cases a similar compression is caused by the shrinking of new connective tissue.

The choked disk of intracranial tumor causes no disturbance of vision for a considerable time, but when vision begins to fail it fails rapidly, until, blindness ensues.

Atrophies of the Optic Nerve.—Post-neuritic atrophy has been

already spoken of as being due to a connective-tissue hyperplasia compressing the nervé-fibers and to disturbances of circulation.

In simple atrophy the connective-tissue portions of the nerve remain unchanged, and the atrophy of the nerve-fibers is brought about by destruction of the neurocytes of origin, or by pressure at some point in the course of the nerve-fibers.

In the ordinary atrophy or gray degeneration the nerve-fibers first lose



FIG. 424.—Types of degeneration of the retinal ganglion-cells in the dog on the third day of quinin poisoning. Nissl stain.

their medullary substance and are then transformed into fine indifferent fibrillæ, often with fatty granular cells scattered among them. At the same time the neuroglia-tissue increases in varying degree.

At present our conceptions of the pathology of the nervous system are undergoing change. The neuron—that is, the neurocyte, with its short

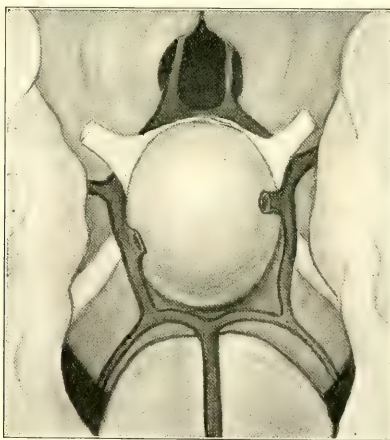


FIG. 425.—Enlarged pituitary body in acromegaly, dividing the chiasm except for a small anterior bundle of fibers

processes and its long axone-process—is now considered to be the nerve unit. The nutrition of the axones is governed chiefly by the ganglion-cell. Disease of the cell is quickly followed by degeneration of the axone, but compression of the axone leads only after the lapse of considerable time to permanent changes in the neurocyte. Many cases of so-called neuritis are now known to consist in a primary disease of the neurocytes of origin of the

nerve-fibers, followed by secondary changes in the tissue supporting the axones.

Simple atrophies of the optic nerve, such as those occurring in tabes, are now thought to be due primarily to disease of the ganglion-cells of the retina, whose axones make up the bulk of the optic nerve. The optic nerve atrophy in Tay's disease of the macula lutea is consecutive to cloudy swelling and degeneration of the neurocytes of the retina. Quinin amblyopia is due to a degeneration of the neurocytes of the retina from the acute ischemia brought about by the constriction of the retinal arteries (Fig. 424). Probably many of the acute toxic amblyopias are due principally to nutritive disturbances in the retinal neurocytes, and the retrobulbar neuritis that has been credited with these changes requires further study.

The diminution of vision in cases of choked disk is perhaps due rather to the nutritive disturbances in the neurocytes of the retina from ischemia in consequence of constriction of the retinal arteries than to the compression of the fibers of the optic nerve. Long-continued pressure on the optic nerve, however, will cause a degeneration of the nerve-fibers that finally involves the cells of origin. Thus, in an advanced case of acromegaly with compression of the optic nerves between the enlarged pituitary body and the atheromatous anterior cerebral arteries (Fig. 425), one nerve being completely atrophic, the ganglion-cells of the retina of the corresponding eye had disappeared entirely.

Tubercle and gumma are sometimes found in the optic disk or further back in the nerve.

Tumors.—Optic nerve tumors are, in general, rare. In the disk one occasionally sees groups of little lustrous globules which resemble the colloid excrescences on the lamina vitrea both in their lamellar structure and in their staining qualities. But they are not surrounded by pigment-cells, and they frequently occur without disease of the choroid or retina, and therefore cannot, like the excrescences on the lamina vitrea, be considered as products of the pigment-epithelium (Fig. 426). The disk is frequently invaded by sarcoma extending from the choroid or from the retrobulbar portion of the nerve, and even more frequently by the extension of glioma of the retina. Metastatic carcinoma of the nerve has been observed a few times, and a few cases of primary glioma are on record.



FIG. 426.—Hyaline bodies in the nerve-head. $\times 10$.

The primary malignant tumors of the nerve, which for the most part are tumors of its sheaths, lie within the dural sheath and involve the septa of the nerve, but usually affect the nerve-fibers merely by compressing them. They belong mostly to the sarcoma-group and occur usually in young persons. They are much less malignant than diffuse sarcoma of the orbit, since they have little tendency to spread laterally, and they are not likely to recur after removal. Clinically they are differentiated from tumors outside the muscle-cone by the fact that they push the eye straight forward, but do not limit its excursions in any direction.

Sarcoma of the nerve-sheaths may be of various histologic varieties, but the main groups are two: myxosarcoma and alveolar sarcoma. The former is composed of spindle-cells and contains foci of myxomatous degeneration.

The latter is composed of epithelioid cells arranged in groups which are separated by connective-tissue septa. The alveolar form of sarcoma was formerly described as carcinoma, and is now described indifferently as fibrosarcoma, alveolar sarcoma, and endothelioma. It may be noted that a purely cellular sarcoma of the choroid may assume an alveolar structure when it extends into the nerve-sheath (Panas); and, conversely, an alveolar sarcoma of the nerve-sheath may assume a purely cellular structure after invading the optic disk and retina (Finlay).

COLOBOMA.

The retina and pigment-epithelium develop from the secondary optic vesicle, which gives form to the growing eye, and about which are molded the choroid and sclera. When the inferior cleft in the secondary optic vesicle does not close, the retina and pigment-epithelium will be wanting here, and, furthermore, the choroid and sclera will be imperfectly developed. The closure of the cleft, however, may sometimes merely be delayed and be accomplished later, so that both retina and pigment-epithelium will finally be complete, but the choroid, owing to the delay in closure, will not be properly developed, and the pigment-epithelium overlying it will not take on its pigment. Thus, in cases of coloboma that are clinically similar in appearance there may be marked differences in histologic structure. The choroid is always rudimentary, the pigment-epithelium always lacks pigment, while the retina and pigment-epithelium otherwise either may be well developed or they may be represented merely by a thin fibrous membrane. The sclera over the coloboma may have its normal curvature, or it may be thin and ectatic. Since the cleft in the secondary vesicle extends back into the optic stalk, if the cleft fails to close posteriorly, a coloboma of the nerve-sheath results; while if it fails to close in its middle portion, the ordinary inferior coloboma of the choroid results; and if it fails to close anteriorly, the iris, which develops from this part, becomes affected with a coloboma.

For the failure of the cleft to close, the following mechanical explanation has been offered: Delicate mesoblastic tissue pushes through the cleft at an early stage to enter the vitreous cavity, while the external mesoblastic tissue, which is continuous with that in the vitreous cavity, grows denser to form the outer coats of the eye. But if the mesoblastic tissue in the cleft also becomes denser, the margins of the cleft will not unite, since they cannot cut through this tissue.

At times, lack of closure of the cleft may be due to fetal inflammation. Inflammation is also held to be responsible for the production of the so-called coloboma of the macula, and coloboma in directions other than downward.

Coloboma of the iris, when not downward, is now considered to be a partial aniridia, also due to fetal inflammation, it being supposed that the periphery of the lens becomes adherent to the cornea before the iris is formed, thus preventing the development of the iris at the seat of the adhesion, and, if the adhesion is circular and complete, leading not merely to coloboma, but to total aniridia.

With coloboma of the choroid there is frequently associated a staphyloma of the overlying sclera, and this ectasia, particularly in cases of microphthalmus, is often very great. The staphyloma may then form a cyst as large

as the eyeball itself, consisting of an outer fibrous and an inner retinal layer. In rare cases the cyst may even lie some distance from the eyeball, the two being united by a tubular stalk—a condition several times described of late as microphthalmus with lower-lid cyst. The stalk connecting the cavities of the eye with the cavity of the cyst is formed of an outgrowth of retina, the retina also continuing into the cyst as its lining membrane, and being sometimes normal in position and sometimes inverted. The cases in which the retinal layer of the cyst is in normal position may be explained by the original theory offered by Arlt, who first studied this condition. He surmised that the intra-ocular pressure caused the eyeball to yield at its weak point, and that the retina proliferated to form a lining for the cystic cavity so produced. But for the cysts with an inverted retinal lining layer, the rod and cones pointing inward, another explanation was offered by Kundrat, and afterward accepted, somewhat modified, by all who have since examined cases of this sort. The primary optic vesicle normally becomes involuted anteriorly and below, so that the lower wall comes to lie in contact with the upper wall. In the cystic cases it is supposed that this original involution of the primary vesicle is incomplete, and a certain portion of this lower wall which later forms the retina, instead of being forced upward into the cavity of the primary optic vesicle, bulges down into the mesoblastic tissue below, a cyst thus being formed with a lining of rudimentary retina in an inverted position.

GLAUCOMA.

Primary glaucoma attacks chiefly hyperopic eyes which have small corneas and shallow anterior chambers, and the patient, as a rule, has general arteriosclerosis. The histologic changes in eyes with established glaucoma have been most thoroughly studied and are well known. Still, it has been difficult to say exactly what changes are the cause of increased tension and what the results. In some cases of secondary glaucoma the sequence of the processes leading up to an established glaucoma can be followed fairly well; in some cases of inflammatory glaucoma also a plausible explanation of the cause of the increased tension can be given; but the etiology of simple glaucoma, as respects the initial pathologic process, is still entirely obscure. In general it is known that if the outflow of the aqueous humor is impeded, the tension rises and the glaucomatous state is established; it is also known that in the great majority of glaucomatous eyes either the filtration angle is blocked or the aqueous humor is so albuminous as to filter with difficulty; and, finally, we recognize that the *rationale* of most of the operations for glaucoma is the reopening of the filtration angle.

The permeability of the filtration angle may at times be diminished by sclerotic changes in the ligamentum pectinatum, but the usual obstruction is due to the pressing of the periphery of the iris against the cornea. This condition may be brought about by the traction on the iris from an anterior synechia, by the forcing forward of the iris in cases of circular posterior synechia from the pressure of the aqueous humor behind, and by the direct pressure of the ciliary processes when they are acutely congested. For a time the iris merely lies in contact with the cornea, but later it becomes permanently attached by inflammatory adhesions.

The consecutive changes found in acute inflammatory glaucoma are as follows: The parenchyma of the cornea is edematous, and small globules of liquid lying among the epithelial cells render the epithelial layer cloudy and irregular. The entire uveal tract is in a state of inflammatory edema, and the retina is edematous and infiltrated in its inner layers. At a later stage the cornea is still edematous, and a sort of pannus may have developed. The sclera has lost its elasticity in part, or it may be thinned and bulging at various points. The lens is cataractous. The iris is atrophic, its pigment-layer may have been drawn round its pupillary margin onto its anterior surface, and its periphery is firmly united to the cornea. The ciliary processes and the superficial portion of the ciliary body are atrophic, and the ciliary body as a whole is flattened. The choroid is atrophic and its vessels are frequently sclerosed, while obstructive changes may be found about the venæ vorticossæ, where they pass out through the sclera. The retina is atrophic in its inner layers, its vessels are sclerosed, and hemorrhages frequently occur. The ganglion-cells and nerve-fibers near sclerosed arteries may be entirely atrophic, and the optic nerve will then exhibit the simple atrophy of ascending degeneration, while the bulging backward of the lamina cribrosa causes a total cupping of the disk. Most of these late atrophic conditions are similar to those found in chronic inflammation of the uveal tract occurring without increase in tension, and therefore cannot be regarded as characteristic of glaucoma.

THE LENS.

The epithelial cells which line the anterior capsule of the lens in a single layer extend back a short distance behind the equator of the lens, and there gradually pass over, through transition forms, into lens-fibers. The epithelial cells are capable of proliferation and development; the lens-fibers, originally formed from epithelial cells, having reached their full development, are capable only of degeneration. Proliferation of the epithelium produces capsular cataract; degeneration of the fibers produces lenticular cataract. These two varieties of cataract may be associated, or each may appear alone.

Capsular Cataract.—Capsular cataract may be brought about by a penetrating injury of the lens, and it then develops at the point of penetration, and is usually associated with lenticular cataract. Uncomplicated capsular cataract is, however, usually brought about by the pressure of the lens against the cornea, after the latter has been perforated and the aqueous humor has escaped. The etiology of congenital capsular cataract is unknown, but the acquired form, as seen clinically, is usually due to the perforation of the cornea from ulceration, and capsular cataract is found uniformly in eyes with corneal staphyloma. *Blennorrhœa neonatorum* sometimes gives rise to central capsular cataract, it would seem, even when the cornea has not been perforated by ulceration.

The ordinary form occupies an area a few millimeters in diameter about the anterior pole of the lens. The epithelium at this point proliferates and forms a layer several cells deep (Fig. 427). These new cells, with processes uniting them to the older cells, soon assume a spindle-form, and make up a mass of superimposed spindle-cells lying just beneath the irregularly elevated capsule and having a continuous layer of ordinary epithelium between them

and the lens-fibers (Fig. 428). In the course of a few weeks the cataract attains a thickness of about ten times that of the lens-capsule, after which it ceases to grow. It now consists of stratified tissue resembling fibrous tissue and containing few nuclei. The layer of epithelium beneath the cataract may, in the course of months or years, secrete a new capsule, so that



FIG. 427.—Beginning traumatic cataract after perforating injury: *a*, perforation in anterior capsule; *b*, new layer of formative cells; *c*, lens-capsule; *d*, layer of subcapsular epithelium, proliferating near the injury; *e*, fatty globules, and *f*, myelin-globules in clefts between the lens-fibers, the latter swollen and infiltrated with leukocytes. $\times 75$.

the ultimate appearance of a capsular cataract will be an apparent splitting of the capsule into two layers, with a growth resembling fibrous tissue between them.

Besides the changes which the epithelium undergoes at the anterior pole of the lens, less marked changes are seen occasionally behind the equator.

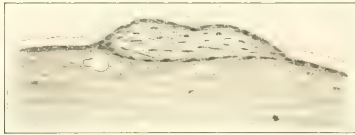


FIG. 428.—Capsular cataract of a few weeks' growth. The proliferated epithelial cells have become spindle-shaped. $\times 75$.

Here also there may be proliferation, the new epithelial cells pushing in between the fibers and the capsule until the posterior capsule comes to be lined like the normal anterior capsule—with a single stratum of epithelium. The process may go even further, but then the posterior cells, instead of

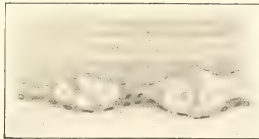


FIG. 429.—Proliferated epithelium lining the posterior capsule of the lens, with numbers of vesicular cells. $\times 75$.

becoming spindle-shaped and forming fibers, as in the case of anterior polar cataract, swell up into great vesicular cells. A continuous layer of these vesicular cells will sometimes be found between the fibers and the new layer of posterior epithelium (Fig. 429).

Secondary cataract after absorption or extraction is brought about

usually in a similar way. Epithelial cells which remain in the equatorial fold of the collapsed capsule proliferate and give rise to short swollen fibers and vesicular cells. In this way an opaque mass is formed which is at first confined to the periphery of the capsule, but later encroaches on the central portion.

Lenticular Cataract.—The normal lens contains a certain amount of liquid, and there is always an accumulation between the posterior capsule and the fibers, so that when a normal lens is examined microscopically there are always to be found in this location numbers of clear globules of myelin coagulated by the methods of preparation.

Senile Cataract.—The initial step in the formation of ordinary senile cataract is the drawing apart of some of the lamellæ near the equator of the lens, and the filling with liquid of the clefts thus formed. The separation of the lamellæ is explained in the following way: The lens up to a late stage of embryonic life is spheroidal, but after the tense zonula has developed, the traction which it exerts helps to bring about the later biconvex form of the lens, a transformation which is favored by the continued deposition of new fibers about the equator. This traction on the superficial lamellæ, opposed by the continued shrinking of the nucleus in old age, facilitates the separation of the cortical lamellæ from the denser nucleus. Following the formation of the clefts, the fibers of the cortex begin to swell from imbibition, frequently acquiring the appearance of vesicular cells, and the liquid in the lens increases. The lens-fibers now exhibit a fine stippling which later becomes coarser, and is then seen to be due to the presence of small globules in the fibers. As these globules increase in size, numbers of clear, homogeneous, myelin-globules and granular fatty globules make their appearance in the clefts between the lamellæ. After this the superficial fibers separate from the capsule, and the cortex becomes a pulpy or semi-liquid mass composed of bits of partially disintegrated fibers, myeline and fatty globules, chalky granules, and liquid. The cataract is then said to be in the stage of tumefaction. An absorption of the liquid then begins, and the lens shrinks to its normal size, when the cataract is said to be ripe. The lens-structures may degenerate still further, and the cataract is then said to be over-ripe. The whole cortex may now have broken down to form a milky liquid in which the nucleus floats (Morgagnian cataract), or the liquid may all be absorbed, leaving only the nucleus in the capsule (membranous cataract).

Occasionally the cortex becomes condensed like the nucleus, and black cataract results. And in old people there is frequently, besides the physiologic condensation of the nucleus, a pathologic nuclear sclerosis, with or without opacity of the cortex, increasing the refractive power of the eye about three diopters. In over-ripe cataracts a capsular cataract usually develops also, but in some cases the capsular epithelium, instead of proliferating, atrophies.

Nonsenile Cataract.—Diseases of the choroid or retina are frequently followed by a cortical opacity at the posterior pole of the lens, which spreads in a star-shaped figure toward the equator. This process can be followed particularly well in animals to which naphthalin has been administered, the fundus disturbances caused by the naphthalin being speedily followed by cataract. Membranous formations in the vitreous resting on the posterior capsule may cause corresponding patches of opacity in the cortex; and,

indeed, senile cataract is supposed in a general way to be due to disturbances in the nutritive supply of the lens. Cataract formation due to cyclitis has been spoken of on page 1184.

Diabetic cataract commences at the poles of the lens and spreads toward the equator, maturing rapidly. The lens-fibers swell, become granular, and break down, and the subcapsular epithelial cells degenerate and atrophy. It having been found that a lens with intact capsule when placed in a solution of sugar or salt immediately became opaque from dehydration, but when placed again in pure water regained its transparency, this explanation was thought to hold good for diabetic cataract also. But the aqueous humor in diabetes contains too little sugar to produce cataract by dehydration, and this explanation has now been given up. It is known, however, that the pigment epithelial cells of the posterior surface of the iris undergo peculiar changes in diabetes, the cells of the posterior stratum swelling and lengthening out into great cylindric cells with clubbed ends, resembling the swollen lens-fibers in beginning cataract (Fig. 430). Furthermore, the cells of the pars ciliaris retinæ, which represent the unpigmented continuation of the layer of affected iris-cells, are, in the anterior portion of the ciliary body, broader than normal and have faintly staining nuclei. Thus the aqueous humor in diabetes would seem to exercise a specific influence upon the epithelial structures with which it comes in contact, producing swelling



FIG. 430.—Alterations in the posterior pigment-layer of the iris occurring in diabetes. $\times 175$.

and degeneration of the elements, which, in the case of the lens, produces cataract.

Lamellar cataract is an opaque zone in the lens between the cortex and the nucleus, which is most frequently seen in rachitic children, and usually remains stationary through middle life. Both eyes are affected. The lens is usually small, and the opacity is due to minute clefts between the fibers, filled with liquid, and to globules within the fibers.

Traumatic Cataract.—After a perforating injury of the anterior capsule a combined form of cataract is frequently seen, varying somewhat according to the extent of the capsular rupture. A limited rupture may be covered by the iris or closed by the rapid development of a capsular cataract, and if but little aqueous humor has gained entrance to the fibers, only a small localized opacity may result, and this may even clear up later. If the rupture is extensive the capsule wrinkles and retracts, and the fibers near the rupture at once become opaque, swell, and protrude through the perforation. When the protruding portion becomes absorbed or detached, other fibers in their turn swell and protrude, so that finally, if the nucleus is not too hard, the entire substance of the lens is absorbed. After a perforation of the capsule, leukocytes may pass into the lens and wander in the clefts between the fibers and in the substance of the fibers themselves. New vascular connective tissue also may enter through the perforation and give

rise to a fibrous cataract, in which, later, chalk may be deposited or true bone form (Fig. 431).

Concussion of the ball may cause rupture of the capsule near the equator



FIG. 431.—Ossification of lens and of cyclitic membrane in an atrophic eye: *a*, atrophic iris; *b*, bone in cyclitic membrane.

of the lens, and intra-ocular tumors may distort the lens and ultimately perforate its capsule.

Congenital Anomalies.—There are numerous clinical forms of congenital partial cataract, frequently having regular geometric forms, and usually symmetric in the two eyes. Distinct from these lenticular opacities are the deposits on the outer surface of the capsule, composed of unabsorbed portions of the fetal vascular system. The hyaloid artery, up to a late stage of fetal life, runs from the optic disk to the posterior pole of the lens, and there breaks up into a number of minute vessels which radiate toward the equator of the lens and converge again on its anterior surface, whence larger afferent vessels pass over into the anterior surface of the iris. Any portion of this vascular system may remain permanently in the form of cords or membranes. Thus, besides membranous patches on the optic disk and persistent hyaloid artery, there may be membranous deposits on the capsule at the posterior pole of the lens, known as posterior polar cataract,

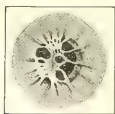


FIG. 432.—Extreme type of persistent pupillary membrane.

which may be associated with remains of the radiating vessels on the posterior capsule. On the anterior capsule there may be a thin membrane, or, more rarely, a circular membrane with an elevated margin from which bands and fibers pass out to the anterior surface of the iris in the region of the minor arterial circle (Fig. 432). These persistent pupillary membranes and the deposits known as posterior polar cataract are to be distinguished from inflammatory membranes, which they may resemble, and also from intracapsular opacities.

Congenital luxation of the lens and coloboma of the lens are both due to the same developmental anomalies. In the half-grown embryo the lens is spheroidal, and fills up a much larger space in the eyeball than it does later. Hence the ciliary body at its inception lies in contact with the sheath of the lens on all sides. Later, with the growth of the eyeball, the ciliary body is drawn away from the lens, and their only remaining connection is through the medium of the zonula fibers. These fibers exert a considerable traction on the lens, holding it in place and flattening it in an anteroposterior direction. If now the fetal cleft has not closed or has closed late, the zonula-

fibers will sometimes not be properly developed inferiorly, and will be lacking either in number or in resistance. The superior fibers will then draw the lens upward, producing the usual form of ectopia lentis. At the same time the inferior fibers may not exert their customary flattening influence upon the lens, and its inferior border, instead of being convex, remains straight or even becomes concave. Besides the usual cases of upward luxation of the lens with downward coloboma of iris and lens, there are others which are not so readily explained: the coloboma being in other directions than downward, or coloboma of the lens existing without coloboma of the iris. In these cases there is frequently persistent pupillary membrane, and often also a persistent fibrous band occupying the position of the obliterated hyaloid artery (see *supra*), and running from the disk to the posterior pole of the lens and continuing along the posterior surface of, the lens to be inserted finally into the sclerocorneal junction. This band has been thought by some to stand in genetic relation with the coloboma.

Lenticonus posterior has recently been explained by Hess, who has examined several lenses exhibiting abnormal curvature of the posterior surface. The conical ectasia is due, he finds, to an early displacement of the nucleus backward, it becoming adherent to the lens-capsule. The capsule then becoming ruptured, the new developing fibers protrude through the perforation and lie in a mass on the posterior surface of the capsule.

THE VITREOUS BODY.

The vitreous body serves, like the aqueous humor, as a passive receptacle for exudations thrown out from other parts; and, again, when infected primarily the vitreous body becomes, like the nonvascular cornea, the seat of an active infiltration, cells from neighboring vascular parts being drawn by chemotaxis toward the point of infection. It is proper to speak of cases in the latter category as true inflammation of the vitreous, which is a rare disease. Finally the vitreous, after the slightest lesion, may undergo fibrillar degeneration with fluidification.

The exudation thrown out into the vitreous may be serous, fibrinocellular, or purulent. The fibrinocellular exudations may rest on the surface of the retina and ciliary body, or may float free as membranous opacities in the vitreous. In cases of acute inflammation the fibrinocellular exudations commonly undergo absorption, while in chronic inflammations they often become organized into connective-tissue membranes which are permanent. In Fig. 416 is shown a permanent membrane of this sort on the surface of the retina, and the membranous formations arising from the ciliary body have been described with cyclitis. There is, however, one form of organized membrane that is sufficiently characteristic to have received the special name *retinitis proliferans*. This is a condition which follows traumatic hemorrhage from the retina, or the recurrent and frequently binocular hemorrhages due to sclerosis of the retinal vessels. A blood-clot lies on the retina, and from this the red corpuscles disappear, new vessels from the retina push out into the remaining fibrin, and connective tissue is gradually produced there; and when the process of organization is once under way it may proceed beyond the limits of the original hemorrhage. Besides the connective-tissue bands and membranes overlying the retina in this affec-

tion, there are degenerative changes in the retina itself, at times with marked hyperplasia of Müller's fibers (Banholzer).

In fibrillar degeneration the fibrillation of the vitreous becomes more marked than in the normal eye, and the coarser fibrillæ contract, causing the body of the vitreous to shrink and be detached from the contiguous structures, while a portion of its liquid is squeezed out and collects between the vitreous body and the membranes of the ball.

Leber was able to produce this condition and subsequent detachment of the retina by injecting simple salt solution into the vitreous, or by introducing an aseptic nonoxidizable foreign body, such as a particle of glass. Usually the condition is brought about by slight affections of the uveal tract, such as those accompanying myopia. Nutritive disturbances may cause crystals of cholesterin to be deposited in the liquid, producing the condition known as *synchysis scintillans*.

Foreign Bodies and Parasites.—Foreign bodies in the eye produce different effects according to their nature and material. Shot that has been fired and gun-caps that have been exploded are usually aseptic, and bits of iron chipped off with a hammer may be sufficiently heated by the blow to become sterilized. Many oxidizable metallic bodies, such as copper and mercury, when introduced into the eye, even if aseptic, cause a noninfective purulent exudation to be thrown out about them; while nonmetallic bodies often lead to the formation about them of granulation-tissue containing giant cells. Foreign bodies which have passed through the vitreous often cause fibrillar degeneration of the vitreous and subsequent detachment of the retina. Chips of iron embedded in the retina lead at length to hemeralopia, contraction of the field, and diminution of vision by bringing about a noninflammatory degeneration of the retina. Iron in the eye also leads to siderosis, a rusty staining of the iris and other tissues, which was formerly considered pathognomonic of the presence of iron, but it is now known that a somewhat similar, though more greenish, stain may be due to the absorption of iron from the blood of intra-ocular hemorrhages.

The *filaria* is a long, slender worm found under the conjunctiva and in the anterior chamber of inhabitants of the West Coast of Africa.

The vesicles of the *Cysticercus cellulosæ* are found particularly beneath the conjunctiva and behind the retina, but are rarely seen, except in inhabitants of Northern Germany.

THE EAR.¹

THE AURICLE.

THE auricle is subject to many affections, of which only part can be mentioned. Thus we find congenital malformations (microtia, macrotia), cutaneous diseases (eczema, herpes), inflammatory conditions (furuncles, varicosities during pregnancy), tumors, benign and malignant (keloid, chondroma, lipoma, angioma, sarcoma, epithelioma, etc.), tuberculosis, syphilis, actinomycosis, and leprosy, as well as cysts, calcareous deposits, ossifications from freezing, necrosis, and so forth, all of which vary so little in their pathology, except as influenced by the cartilaginous tissues of the auricle, from similar affections on the rest of the body, and which are described elsewhere in this book, that they may here be passed over by title only. Attention should be called especially to pathologic effusion of serum between the perichondrium and cartilage, separating them and terminating in suppuration. This is occasionally syphilitic in origin. There also occurs at times a true perichondritis serosa, the fluid arising from the cartilage or perichondrium.

Hematoma auris is an effusion of blood beneath the perichondrium, or into the cartilage which is then separated from the former or ruptured from its base. It is oftenest seen in the insane, the brain lesion favoring rupture of the blood-vessels on account of the increased pressure, (intense mental excitement), but occurs also in leukemia and other diseases with impoverished blood, as well as after injuries. We often find degeneration of the cartilaginous cells, new blood-vessels, and later on degenerative areas in the cartilage itself. The blood in hematoma may contain the *Staphylococcus pyogenes aureus*, and hematomas have been observed extending into the meatus and containing a thick fluid.

Congenital atresia of the external meatus may exhibit itself as a part of rudimentary development of the ear, and is generally accompanied with a rudimentary tympanum and organs for the conduction of sound to the inner ear, rarely with deeper-seated defects in the labyrinth. Acquired atresia may depend on injuries or on croupous or diphtheric membranes invading the meatus and extending to its termination.

THE MEATUS.

Hyperemia of the meatal walls may be due to associated inflammation or disease or injury of the auricle, to careless insertion of specula for examination, or to rude attempts to remove foreign bodies lying further in.

¹ This paper is founded on the valuable pathologic sections of Dench's excellent *Text-book on Diseases of the Ear* (1895), and additional annotations to date from contemporary etiologic literature.



FIG. 433.—Hematoma (after Jacobson).

The chief foci of inflammation in **circumscribed external otitis** are found in the outer portion of the meatus, because the glands are there more numerous, but any part may be affected. The abscesses occur in crops from inoculation of different glands in succession. Before one is healed another may have been infected, so that attacks may last for weeks. If the small abscesses that form fail to discharge, the glands become fibrous nodules. Occasionally the cartilage is softened without involvement of the glands or the perichondrium is affected. The infection depends on local abrasions or enters along the hair-ducts. Salt water or cold water or the use of astringent lotions may excite furunculosis. All attacks are actually attacks of lymphangitis with adenitis of postauricular glands simulating mastoiditis.

Trophic irritation from pathologic affections of the nerves of the meatus may excite so-called sympathetic furunculosis in the opposite ear. If an attack occurs in the second meatus in a healthy patient, and there is no local abrasion or assignable cause, the case may be entitled reflex or sympathetic.

Circumscribed external otitis may become diffuse and extend along the meatus so that there is no distinct line of demarcation between the two forms.

Diffuse external otitis is a different pathologic condition. If mild, there are increased activity of the glands and increased secretion. With eczema the deeper glands are involved and the epithelium is exfoliated. The deeper the infiltration the more abundant the secretion, which, if profuse, washes off the cells, leaving a shiny surface; if slight, it dries and leaves numerous minute crusts in the meatus. Later on, hypertrophy of the underlying membrane and contraction of the meatus appear. This affection may depend on gout or exposure or on acne and seborrhea of the auricle. The bone and membrana tympani, or middle ear, may be attacked finally.

In the more severe forms depending on injuries, foreign bodies, parasites, or circumscribed otitis, the epithelium is more abundantly exfoliated, and there is small-cell infiltration or necrosis. Cases occur in which the pavement-cells enlarge and dilate the meatus and excite mastoiditis by obliteration of the dividing wall.

Croupous and diphtheric external otitis are recognized forms of aural disease, the lesion being the same as of similar membranes elsewhere, modified by the anatomic differences of the parts involved. Diphtheric membranes have been followed from the auricle through the meatus into the middle ear; but the onset of true diphtheric otitis is generally through a perforation in the membrana tympani from the pharynx.

There is a **malignant form** of otitis externa with tendency to metastatic reproduction, and Buck speaks of a true *desquamative form* with repeated exfoliation of epithelium.

Parasitic external otitis begins with hyperemia of the membrana tympani and annulus, and then of the adjacent walls of the meatus. Sometimes the membrana tympani is first attacked by the parasites, resulting in perforation and inflammation of the tympanum; but generally the parasitic inflammation begins this side of the membrana tympani and works its way out, the epidermis degenerating and the parasites attacking it. A *circumscribed* parasitic inflammation has been described, but almost all attacks follow the outward track left behind by oils or fats or even glycerin dropped into the meatus for relief of pain or deafness. The fungi exciting parasitic

otitis have long stems (hyphæ) and cellular transparent globular heads (sporangia), with delicate ribs reaching to the periphery. All forms of aspergillus need a special soil for their development and proliferation in sufficient abundance to excite parasitic otitis.

In addition to the forms of external otitis just described, Dench recognizes an acute form with rapid congestion, free transudation of blood-elements and infiltration of round cells, together with pus in the final stage. The normal rigidity of the tissues in this region generally retards necrosis until a late stage. Furthermore, we hear recently of a tropical form of external otitis resembling furunculosis, but with painless discharge of pus.

Impacted Cerumen.—This depends on increased activity of the glands or irregular shape of the ear-canal, preventing natural exfoliation, or on the habit of trying to cleanse the meatus with ear-sponges, with the result alone of driving the deposit further into the canal. This condition may also be due to reflex action of nasopharyngeal catarrh on the ceruminous glands, as many patients so affected exhibit impacted wax. Or, again, the plug may depend on the presence of cotton or of some small foreign body left forgotten in the meatus, about which the cerumen collects. If a ceruminous obstruction increases in size, the condition may be complicated with desquamated epithelium due to what is really a foreign body. Such a process may erode the walls of the meatus, produce sclerosis of the mastoid-cells, perforate the membrana tympani, and excite alterations in the middle ear. We must not, however, forget that cerumen often collects in old suppurative cases, so that the changes discovered after its removal depend rather on the former process than on the presence of the fresh cerumen.

Foreign Bodies.—The variety of foreign bodies lodged in the meatus is infinite: buttons, nut-shells, sea-shells, seeds, bits of glass, absorbent cotton, lamb's wool, sand, gravel, earth-worms cut into pieces and inserted for relieving earache—in fact, almost everything of proper size. Foreign bodies of any nature can remain in the ear a long time and finally excite inflammation or become the nucleus of a plug of cerumen. Melted lead has been known to run into the meatus; and Sir W. Dalby reports a curious case in which plaster-of-Paris, used for making a mask for a portrait-bust, accidentally ran, when soft, into the meatus, and was extracted only with the greatest difficulty. Many persons use wooden toothpicks to relieve itching in the ear, a piece breaks off, and so enters the list of curious foreign bodies in the ear, and becomes a cause of inflammation. The living larvæ of flies have often been found in this situation, and occasionally a living fly itself has been found, exciting pain and inflammation persisting long after removal.

Exostoses and Hyperostoses.—These occur anywhere in the meatus, but mostly at the meeting of the cartilaginous and bony portions. Most of the growths are flat, with a broad base; others are pedunculated, and sharp or conical growths have been seen. The structure is cancellar



FIG. 434.—Aspergillus: M, mycelium; H, hypha-stalk; R, receptaculum; S, spore (sporangia).

or ivory-like; they are single or multiple, growing sometimes from one side, then from the other, and occasionally from both, but never totally obliterating the meatus. If deafness arises from the presence of such formations, it is due rather to cerumen heaped up alongside them, than from total occlusion of the meatus.

Exostoses are asserted to originate from subperiosteal abscesses making their way into the meatus; but Hartman, for example, in an extensive practice never saw such a pathogenesis. Many authors refer exostoses to gout, inordinate bathing, or to heredity. The latter tendency is more marked in hyperostoses than in exostoses, and according to some a line should be drawn between the two varieties of tumors, because hyperostoses are seen deeper in the ear-canal than exostoses. Both are probably anomalies of development, and have no pathologic connection with inflammation or morbid processes. Such growths may occur simultaneously in both ears.



FIG. 435.—Osteomata.

The meatus may be the seat of a great variety of **neoplasms**, such as fibroma, pedunculated osteosarcoma, carcinoma, papilloma, sebaceous adenomatous cysts, spindle-cell sarcoma, cartilaginous spongy osteoma, and, finally, of chloroma, a pale-green, rare tumor arising mostly in the temporal bone and invading the meatus on its advance toward the middle ear.

Polypi also abound in the meatus, generally arising from granulations dependent on circumscribed abscesses. Of these there are four chief varieties: Mucous, with areolar connective tissue, round and spindle-cells, retention



FIG. 436.—Polypi (after Steudener).

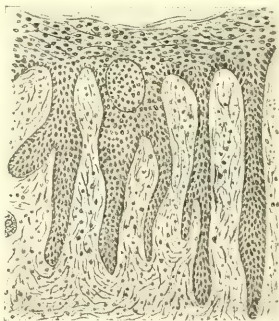


FIG. 437.—Structure of polypi (after Steudener).

cysts, cylindric and pavement epithelium; fibrous, firmer with fewer vessels and cysts but more fibers; myxomatous, gelatinous, with spindle- and star-shaped cells; and angiomatous, vascular with fibrous connective tissue. Some polypi contain hair, while others contain giant-cells and horny epithelial products.

Ozena of the meatus has been lately described, the secretion flowing from the passage resembling that flowing from the nose during true

ozena, being liquid, with minute or larger crusts, and having the characteristic odor of genuine ozena. Syphilitic ulcers, condyloma, tuberculosis, and actinomycosis also occur. In pregnancy acute suppuration associated with a filamentous organism has been described as "pseudoactinomycosis." Fibrous cords have been found stretching across the canal.

THE MEMBRANA TYMPANI.

Injuries of the membrana tympani may be due to the introduction of any pointed instrument, or even to the effect of a sudden kiss on the auricle. If dependent on the entrance of a pointed instrument into the meatus, the rupture is mostly round and in the upper posterior quadrant. If due to rapid condensation of air, from boxing the ears, from work in caissons with condensed air, from forcibly pulling the auricle, from fractures of the skull or too violent massage, or from sneezing or coughing, the rupture lies in the anterior quadrant. Ruptures of the membrana tympani may be single or multiple, slit-like or circular. The concussion from exploding dynamite is said to produce a round perforation. If caused by chemicals, the entire membrane may be eaten away. In basal fractures the annulus may be broken, and as it falls from place the membrane follows and is likewise ruptured. An intestinal worm vomited into the tube has been known to escape from the tympanum by rupturing the drum-head. Bluish discolorations and varices on the membrana tympani, from the projection of the bulb of the jugular into the tympanum, and tumors originating from the edge of a perforation in the membrana tympani, have been from time to time reported.

With rupture, suppuration generally ensues from infection with the end of the instrument, although the common, mostly injurious, instillations of fluids to relieve the pain or to subdue the inflammation caused by the traumatism may produce the same effect. Condensation ruptures, if left to themselves, never suppurate; conical perforations have lately been reported. In a recent case of purpura hæmorrhagica the meatus and membrana tympani exhibited minute hemorrhagic extravasations.

Tubotympanic congestion is characterized by hyperemia of the blood-vessels of the mucosa of the tube, tympanum, and membrana tympani, terminating usually in an abundant secretion of mucus or serum within the tympanum, and mostly without perforation. It may be seen most typically in gout or rheumatism and occasionally in Bright's disease. The venous hyperemia in the membrana tympani is confined to the hammer or periphery. This form of congestion rarely becomes inflammatory. When the attic is involved, Shrapnell's membrane may bulge forward so as to resemble a polypus. Acute myringitis, mentioned by some writers as a distinct affection of the ear, exhibits similar hyperemia of the blood-vessels of the membrana tympani, and is seen during the summer months, when surf-bathing is in vogue, the saltiness of the sea-water, and the force with which it enters the meatus, irritating the membrana tympani and congesting the vessels.

In **catarrh of the tube**, which is a subdivision of aural disease



FIG. 438.—Rupture of the antero-inferior half of the drum-head, caused by a box on the ear (after Politzer).

recognized by a few authors, we find the same lesions as in tubotympanic catarrh, with other changes in the tympanum depending on the aggravated closure of the tube itself. In the tube we have hyperemia and inflammatory swelling of the mucosa, so that, together with the abundant secretion, the tubal walls are closely compressed, producing loss of hearing. Then, too, the tympanic air becoming rarefied, the membrana tympani is pressed in toward or even against the promontory, still further obstructing the hearing. The serum within the tympanum arises more from the epithelial cells than from the rare mucous glands of the middle ear.



FIG. 439.—Tubotympanic effusion: line of fluid as seen through transparent drum-head (Jacobson).

There are cases in which the tube is so patent, or becomes so from atrophy of the mucosa, that sudden changes of air in the nasopharynx may cause concussion of the membrana tympani, with loss of hearing, or even rupture. At times the walls of the tube are rigid and the lumen patent, so that the air during inspiration passes freely into the tympanum, producing autophony. Moreover, rare cases of paralysis and permanent contraction or clonic or tonic spasm of the tubal muscles have been reported together with objectively visible tinnitus. Finally the tube may be obstructed by foreign bodies, exciting deafness or serious inflammation.

THE MIDDLE EAR.

Inflammations.—In acute catarrh of the middle ear there is inflammation of the mucosa, especially in the cellar of the tympanum, although that of the attic may become involved. This condition stimulates the glands, so that the secretion commingled with serum and epithelial cells fills the tympanum to a greater or less degree. The next steps are swelling and exfoliation of the mucosa of the membrana tympani, exposure of the fibrous layer, and perforation, through which the pent-up fluid escapes into the meatus. Perforations may depend on increased pressure within, as much as upon a weakened membrane. The tubal mucosa is often involved in this process, although the chief burden falls upon that of the middle ear and membrana tympani. Sometimes the effusion is only serous, but even that may produce deafness if not promptly evacuated.

When the secretion from otitis media is collected aseptically and quickly examined, only one sort of microbe is found; after perforation has taken place secondary infection of the discharge becomes possible. Consequently the formation of pus often is retarded until perforation occurs; the tympanic fluid may prevent in a measure bacterial invasion. Cases of acute otitis media have been reported from the pus of a pharyngeal abscess passing along the sheath of the tensor tympani muscle. Vice versa, retropharyngeal abscesses may arise from the pus of otitis media following this same muscular sheath.

In acute purulent middle-ear inflammation, as distinguished from the nonpurulent form, there are engorgement and thickening of the mucosa, which more or less fills the tympanum. The congestive stage is followed by profuse exudation of serum and migration of white corpuscles. Necrosis of the walls and ossicles soon ensues, favored in the latter by minute furrows

and lacunæ, lately described by Katz as normally existing in the anvil most of all. This ossicle, owing to its position and its feeble circulation, soonest falls a prey to necrosis. The early stages may exhibit mucous blebs or sacs on the inner surface of the membrana tympani. In the later stages, a localized myringitis may generally be assumed to exist.

When the inflammation is once established the fluid gravitates to the floor of the tympanum, although there have been instances in which the mucosa above was so much swollen that the exudate remained high up in the attic and escaped there through a perforation, surgical or spontaneous.

Dench emphasizes the position of the long process of the anvil, which forms a gutter along which fluids may escape into the lower levels of the tympanum; but if the latter is divided into two apartments by mucous folds, Shrapnell's membrane may bulge forward to an extreme degree.

Attic suppuration may dissect away the soft parts along the upper wall of the meatus, the pus making its way outward and forming a postauricular abscess. The mastoid may become diseased before the abscess forms, so that pus in this region is generally pathognomonic of mastoiditis.

When such an abscess has once been formed the periosteum is detached, and infection takes place into the brain through the sutures, tympanic roof, or along the sinuses. With local caries the pus affects the meninges or enters the blood through the sinuses.

Hemorrhagic exudate into the tympanum has been described also in acute otitis media. Adenoids and nasopharyngeal affections may favor its production, exciting catarrhal and purulent conditions, or they may occlude the tube and hinder drainage, or offer a nidus for bacteria, from which these, under favorable conditions, invade the mucosa of the tympanum. Serous exudates occasionally contain cholesterin. Otitis in infants may produce intestinal complications, and, on the contrary, as claimed by some authors, intestinal disturbances may excite otitis with effusion.

The proliferating, nonsuppurating form of chronic otitis media begins with swelling and hyperemia of the mucosa, exciting the growth of a vascular and cellular tissue, but rarely fibrous. The mucosa, as a whole, is thickened, and the tympanum filled with exudate. The whole district is gradually involved, the membrana tympani thickened, and often filled with chalk deposits. The membrana tympani is occasionally atrophic throughout, but generally thicker or thinner at spots. A further step consists in occlusion of the tube, contraction of the tensor tympani, ankylosis of the various joints of the ossicles, and finally the entire membrana tympani is dragged in toward or even against the promontory. Not only ankylosis but hyperostosis of the ossicles has been reported.

The pathologic changes in the late stages of chronic catarrh (sclerosis) depend on fibrous and osseous ankylosis of the plate of the stapes, pressure upon the labyrinthine endolymph, and interference with the circulation within the entire capsule. Although there is an anastomosis between the vessels of the tympanum and labyrinth, it is so circuitous that pathologic conditions in the latter must rather be ascribed to pressure than to collateral circulatory disturbances.

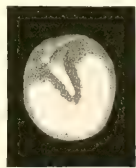


FIG. 440.—Calcareous deposits in the drum-head after middle-ear inflammation.

The tinnitus of which patients complain depends on an infinite variety of causes, such as defective circulation, heart disease, affections of the nerve of hearing, arterial sclerosis in the aged, anomalies of tension in the membrana tympani, tubal contraction, cerumen, contusions of the nerve-filaments, varicose vessels, and fatty degeneration in the nerve, neoplasms in the cochlea, the use of quinin, the salicylates, phenacetin, concussions, diabetes, brain disease, and so on. It is often synchronous with the pulse, even when there are no cardiac defects. Rustling sounds depend on aneurysms, melodies, voices, etc., on cortical irritation or auditory hallucinations. Diplacusis seems, so far, to depend on circumscribed affections in the cochlea. Tabes and syphilis, according to some authors, have no aural symptoms except tinnitus.

Chronic otitis has been referred to dental irritation, as from caries or from defective fillings and consequent irritation of the otic ganglion. Hemorrhagic vesicles on the membrana tympani are asserted to have disappeared on filling certain carious teeth. Otalgia often depends on dental irritation. It is a disputed question whether anemia produces labyrinthine reflexes. Vertigo is not always due to pressure, but to a reflex between nerves of the middle-ear mucosa and the cerebellar centers for equilibrium.

Hyperplastic middle-ear disease is pathologically characterized by increased density in the fibrous portion of the tympanic mucosa, diminished size of the glands, reduced secretion, with new tissue and contraction of the ligaments, resulting in dislocation of ossicles and membrana tympani. Finally there is ankylosis of the ossicular joints or chalky deposits in the oval window. The plate of the stapes is never totally ankylosed. The deafness is never actually proportional to the extent of the ossification, but depends more upon the thickness or thinness of the plate of the stapes when ossification has ensued. Shrapnell's membrane appears shrivelled, but, strange to say, despite an advanced stage of disease and a high degree of deafness, the membrana tympani often looks absolutely normal.

Chronic suppuration in the middle ear depends on necrosis, even if beginning with catarrh alone. The necrosis begins in the connective tissue and extends to the tympanic walls or ossicles. More or less extensive perforation of the membrana tympani rapidly follows. In old cases the upper portion is perforated, and such a perforation indicates caries in the anvil or tympanic roof. In tuberculosis or syphilis loss of bone is rapid. If at all involved, the labyrinth soon succumbs or not at all, for even with both windows covered with pus the labyrinth may remain unchanged for years. Any pathologic alterations then discovered are due more to pressure or adhesions than to infection.

Mastoiditis may be seen in chronic cases, but is rare with good drainage. If the pus is obstructed, it may enter the bone and involve the antrum. Occasionally the cells are obliterated and the bone changed into an ivory-like mass.

True mastoiditis means an extension of suppuration from the middle ear into the mastoid, although a few instances have been reported in which the tympanum was unaffected by disease. Retention symptoms soon ensue, and cerebral complications are likely to occur. If the cranial cavity is invaded by the infection, we have meningitis or abscess; if the blood-vessels are involved, we get thrombosis or brain-abscess. Infection may occur through the sutures, especially the petrosquamous, and, even when pus is

escaping through a postaural abscess, there is an infectious focus remaining in the tympanum and liable to excite cerebral disturbances at any time.

The condition of the middle ear after chronic suppuration has run its course varies in each case. With destruction of the *membrana tympani* there is a hyperemic promontory with edema and some serum. What is left of the *membrana tympani* is thickened and hyperemic, and if, as may happen, fibrous bands or mucous folds have shut off the attic, we find necrosis of the ossicles or attic-walls, cholesteatoma, or possibly some mastoid involvement. If the cavity does not suffer infection, the discharge is not likely to return. Later the ossicles may be lost from caries and total deafness supervene, yet the labyrinth remain intact. The mucosa of the middle ear is sometimes characterized by cystoid spaces, some empty and others filled with degenerated epithelial cells, while the meatus may contain hairy polypi, with giant cells and hair-bulbs. The capsule of such polypi is composed of small cells and connective tissue, but no trace of epidermis. They flourish on the same soil as cholesteatoma.

Chronic suppuration may be followed by facial-nerve paralysis, sarcoma, carcinoma with hyaline degeneration, fibroma, angioma, dehiscences with

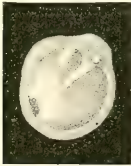


FIG. 441.—Residua of middle-ear suppuration. Nearly total loss of drum-head. Handle of hammer resting on mucosa of promontory.

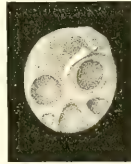


FIG. 442.—Residua of middle-ear suppuration. Transverse section (schematic), showing adhesions of drum-head to promontory. Front view, showing old cicatricial center actions.

fibrous membranes, hyperostosis of the promontory, and sequestra, the latter ultimately aggravating the condition of affairs by giving rise to hyperplasia, sclerosis, and partial or complete obliteration of the mastoid.

Bacterial Invasion of the Middle Ear.—The healthy tympanum, as well as the tube and nasopharynx, may contain bacteria, as has been abundantly proved by recent investigations. The organisms may also reach the tympanum through the lymphatics, or along the vessels, or from localized myringitis. Infants' ears contain innumerable bacteria, to which we may refer the frequency of middle-ear suppuration at this early period of life; for late researches have proved that in 90 per cent. of infants examined postmortem the tympanum contained bacteria. Although many infants so affected died from different exanthemas which might easily have excited suppurative otitis, only 1 in 10 offered aural symptoms during life. Some writers attribute this host of organisms in infants solely to post-mortem alterations.

When fetor is observed, saprophytic organisms are present; they gradually kill off the pathogenic bacteria. When the former lose their vitality, other types appear.

Cholesteatoma.—There is hardly any affection of the ear concerning which so diverse explanations have been offered as cholesteatoma. Some assert that it is a true tumor having no connection with suppuration, for

cases have been observed in apparently normal ears. Others grant that cholesteatoma may occur without suppuration, but say that if the growth becomes infected it changes in nature, becoming caseous, purulent, and covered with epidermis. It is claimed again that cholesteatoma is an epidermoidal transformation of the mucosa of the middle ear, the epidermis of the meatus and membrana tympani attacking the middle-ear mucosa, which has lost its epithelial layer. Some attribute the tumor to epithelial inflammation, and insist that it cannot exist without a peripheral perforation of the membrana tympani; or, if central, then the edges must be adherent to the promontory. The invasion of the tympanum may take place through a mastoid fistula or the posterior osseous meatus-wall. If no perforation can be traced in the membrana tympani, we must positively prove that it never has existed before we can deny that a perforation is indispensable to the development of cholesteatoma. In Leutert's opinion cholesteatoma is an ordinary retention cyst, the pavement epithelium entering the tympanum

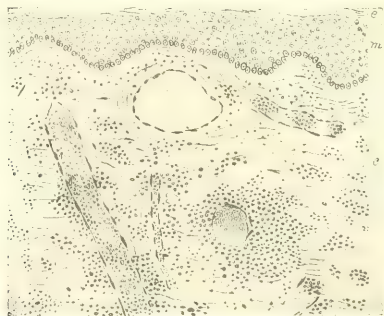


FIG. 443.—Cholesteatoma: *c*, cutis with round-cell infiltration; *m*, Malpighian layer; *e*, epidermis (Steinbrügge).

through a perforation, then developing, and finally becoming capsulated. Steinbrügge thinks that the tumor originates in the rete of the cutis; and Rednew insists that there is a vast variety of such masses, most of which are heterologous tumors, in Virchow's meaning of the term, while the remainder may be divided between retention masses, hyperplastic epidermis, or epithelial cysts.

Large cholesteatoma may erode the surrounding walls and convert the meatus, tympanum, and mastoid into one large cavity. Spontaneous exfoliation of the entire tumor has been observed. If stratification is absent the tumor is in its formative stage. Later, an offensive odor may be considered as pathognomonic of fatty degeneration of the enveloping epithelium.

THE LABYRINTH.

The labyrinth may be the seat of hyperemia, extravasation, and inflammation, primary or secondary. Hyperemia depends on venous obstruction, rupture of vessels, disturbances in the sympathetic, and on chronic middle-ear inflammation and suppuration. When due to venous congestion it

becomes permanent with degenerative softening of the parts affected. Hemorrhages occur in infectious diseases, diseases of the heart and lungs, in tympanic suppuration with caries, and in pachymeningitis. Total degeneration of the district affected generally follows a labyrinthine hemorrhage even if the blood be resorbed. If the vascular injury is slight, we have a temporary mechanical obstruction, the clot becomes organized, and the function may be partially restored. Thrombus or embolus causes anemia and consecutive degeneration unless the circulation is again established. If either is due to infection, septic foci and secondary inflammation may follow.

Primary inflammation of the labyrinth is rare, and the local changes in infectious diseases depend on the invasion of special germs. Pus has often been seen in the aquæductus cochleæ after cerebrospinal meningitis. After chronic middle-ear suppuration and necrosis the labyrinth may become involved through the round window, the vessels or the lymph-spaces, the chief conditions being fatty changes, bony constriction, and fibrous-tissue growth in the round window. A fatty tissue with dilated vessels and extravasations of blood is seen sometimes in the tendon of the tensor tympani in the tympanic mucosa. New tissue also forms about the stapes-plate, and atrophy in the lower convolutions of the cochlea.

Acute otitis media rarely attacks the labyrinth, as the process is generally too short to extend very deep, and whatever changes are found remain limited to that part nearest to the round window.

Ménière's disease is characterized by exudates with sclerosis of the arteries, partial occlusion of the lymph-channels, hemorrhages, impaired mobility of the window membranes, and increased tension in the endolymph. Leukemia exhibits petechiæ, new tissue formation, ossification in the scalæ and semicircular canals, and infiltration of the auditory nerve. Syphilis contracts the labyrinthine spaces by otitis and hyperostosis, and leads to atrophy of the ganglionic cells, thickening of the lining periosteum, and formations of chalk. Endarteritis has also been seen with circulatory disturbances, and increased tension probably due to exudates (though none like those in syphilitic iritis have yet been shown), impairing nutrition and exciting necrosis or inflammatory softening, as in gumma. In tertiary syphilis labyrinthine affections are bilateral, the auditory nerve being simultaneously affected, while there may be affections of hearing, which have been entitled epilepsy of the ear. Syphilis may, however, have no other aural symptoms than tinnitus. Congenital syphilis may affect the labyrinth in the same way as acquired. So, too, chronic alcoholism exhibits aural symptoms suggesting temporary exudates or alcoholic neuritis. In regional carcinoma the cochlea and semicircular canals contain hyaline cells with free hyaline drops, or cavities containing hyaline cartilage which may be a precursor of caries, or transformation of the cartilaginous cells.

Primary tuberculosis of the labyrinth has not yet been proved, but secondarily there are fibrous formations, necrosis, ossification of the capsule, and depression of Reissner's and Corti's membranes.

Deafness of the aged has been examined pathologically so far in women, mostly, and has resulted in establishing atrophy of the ossicles, infiltration and chalky degeneration in the articulations, ossification at the base of the stapes, and pressure-changes in the lower whorls of the cochlea. Diplacusis may depend on labyrinthine pressure, but, as most patients so affected suffer from chronic otitis, this phenomenon may be properly referred to anomalies

of tension in the membrana tympani reacting on the auditory nerve through the fifth pair.

A curious labyrinthine observation has lately been reported in which, in patients so affected, testing with high tones has produced a handwriting pathognomonic of writer's cramp, while the testing of low tones made the handwriting unsteady, like that of old age.

AURAL LESIONS IN CONSTITUTIONAL DISEASES AND OTHER CONDITIONS.

Measles shows hyperemia of the mucosa, but not much swelling, tenacious exudate in the tube and pharyngeal orifice, in the tympanum and around the oval window, hemorrhages in the middle of the tube, and similar extravasations and an exudate on the inner surface of the membrana tympani. All this may represent an extension through the tube or a purely local disease. The tympanum may be involved without pathologic appearances upon the membrana tympani. Almost every case of measles has otitic complications; perforations are rare. The bacteria most often found are streptococci. The protracted course of otitis from measles is due to its mildness, though the attack may not reach its maximum until the exanthem has disappeared. Bezold insists that otitis is an integral lesion of measles. The normal condition of the tube, in his experience, makes tubal extension improbable; while the punctate hyperemia, the ecchymoses, and the granulations compel us to regard otitis as a genuine local manifestation of the exanthema.

Mumps.—Mumps often attacks the ears, affecting first the parotids and then the middle ear and labyrinth. The middle-ear lesion is trifling, that of the labyrinth severe, involving either the semicircular canals or the cochlea or both with extensive serous exudates, and seriously impairing the hearing.

Rheumatism.—Uchermann insists that there is a distinct form of middle-ear disease due to rheumatism, with acute swelling of the mucosa, severe pain, and a serous whitish or yellowish effusion into the tympanum, and finally sclerosis in chronic cases, with affection of the ossicles, ossicular ligaments, and labyrinth. The diagnosis of acute otitis media without apparent cause from one of actual rheumatic origin might be made from the disappearance of the latter after a course of salicylates. It is still a disputed question whether or not the ear may be affected in acute articular rheumatism alone or equally in both the acute and chronic forms. Some writers claim a whitish exudate in the acute form and a yellowish in the chronic. Exacerbations of pain in the ear during acute rheumatism may indicate fresh inflammation of the mucosa and effusion. Aged rheumatic patients are often very deaf and suffer from a blowing sort of tinnitus and loss of low tones. The labyrinthine lesions in such rheumatic cases consists in periostitis in the semicircular canals and vestibule, with consequent pressure-changes. Gout may act similarly.

Tuberculosis.—Tuberculosis of the mastoid has been known, but generally the middle ear is mostly affected. Some claim that the invasion of the middle ear takes place through the mastoid or from the postauricular glands; others, that it originates in the lungs, and, if there is nasal obstruction and consequent nasopharyngeal catarrh, the infection takes place through

the tube. Glandular swellings around the ear indicate local tuberculosis, and the discharge may then be examined for bacilli. Invasion of the middle ear has been known to follow the exhibition of new tuberculin. *More cases of primary tuberculosis of the ear occur than are probably recognized as such.* Many writers argue that tuberculosis of the mastoid and middle ear is common, at all events in the late stages of visceral tuberculosis. The chief characteristics are numerous yellowish nodules in the mucous layer of the membrana tympani, multiple perforations without much pain, an adherent membrane with bacilli upon the promontory and extending over the entire tympanic mucosa, and a scanty discharge with rapid bony destruction. The round window may be closed with fatty tissue or with connective tissue containing fatty elements. The absence of bacilli does not exclude tuberculosis, for these micro-organisms may escape detection. Again, there may be no bacilli discoverable, yet inoculations and the subsequent history prove that tuberculosis was at that time actually at hand within the ear. The handle of the hammer is lost in the later stages. Optic neuritis has been observed in connection with aural tuberculosis. Seven per cent. of all tuberculous patients have aural symptoms; and latent tuberculosis of the tonsil, whence it might extend to the middle ear, is by no means rare.

Nephritis.—It is asserted that about 5 per cent. of all the patients affected with Bright's disease sooner or later become deaf, and that the loss of hearing may be an initial symptom of nephritis, just as loss of sight. The process consists in hemorrhages into the mucosa and tympanum, with loss of high tones resulting from alterations in the first convolution of the cochlea. As cerebral apoplexies are not unusual in Bright's disease, we may suspect interruption of conduction along the auditory nerves or in the auditory tracts. It is alleged that, if the renal disease improves, the hearing, if affected, may also improve. The vertigo in this affection may depend on albuminuric degeneration of the labyrinthian nerve-filaments, analogous to albuminuric retinitis. The tinnitus and deafness of uremia have been referred to edema in the sheath of the auditory nerve.

Myxedema.—Myxedema excites hyperemia in the middle ear, and the alleged diminution of deafness in patients during the thyroid treatment of myxedema has led to the thyroid treatment of deafness.

Diphtheria.—Diphtheric membranes have been seen extending into the middle ear from the auricle and meatus, but true diphtheric otitis mostly results from a perforation in the membrana tympani, with bacilli in the discharge. In 24 autopsies after diphtheria, the ear was involved in all but 2. Such extension may be overlooked, owing to severity of constitutional symptoms. Perforation is rather rare. Although the tube may contain the specific membrane, and the tympanum the typical bacilli, it is asserted by some authorities that the aural manifestation is not a genuine ear disease, but solely a local manifestation of general infection. The bacilli may remain in the middle ear long after the pharyngeal diphtheria has disappeared. We may find pseudodiphtheria of the ear with streptococci.

Meningitis.—Cerebrospinal meningitis affects the labyrinth and is an important cause of deaf-mutism, the specific lesion consisting in pressure on the auditory nerve from exudates, diseases of the nerve-sheath and nerve-centers. Neither the labyrinthine capsule nor the nerve is ever wholly destroyed.

Influenza has produced new types of ear disease with bacilli, hyperemia of the mucosa, thick, glairy secretion, hemorrhagic exudate, pustules, bag-like proliferation of the membrana tympani, and involvement of the mastoid. One type is marked by circular hemorrhages on the membrana tympani after copper-colored granulations on its mucosa, changing later to panther-skin patches. Mastoiditis occurs in one-fifth of all influenza suppurations of the ear, attacking the diploë first and then the cells. One great characteristic is the vast extent to which the mastoid may be involved without much pain. Influenza bacilli have been found in infantile otitis, but sometimes associated with former suppuration. Influenza produces more cases of mastoiditis requiring operation than any other constitutional disease.

Other Diseases, etc.—Typhoid bacilli have been seen in mastoiditis after typical typhoid fever.

Pneumonia or bronchopneumonia may excite otitis media in children, and the pus occasionally contains pneumococci. Leukemia has been followed by isolated affection of the auditory nerve, and hemorrhages into the vestibule and first cochlear convolution. Agoraphobia may have a sympathetic affection of the middle ear simulating aural vertigo. Tabes may be associated with auditory-nerve deafness and atrophy of the middle-ear mucosa. The auditory tracts may also be affected, beginning in the nerve-terminals, analogous to tabic atrophy of the peripheric sensory nerves.

The middle ear of ill-nourished infants is markedly subject to otitis with exudates and often with pus, though perforations are rare. Even with pus in the tympanum the membrana tympani does not project. Infection is due to vomiting of indigestible food, coryza, extension of specific inflammations, and anemia; while the lowered resistance of the mucosa and the anatomic relations of the parts permit free growth of germs. But the pathologic condition is no absolute proof of bacterial origin of the otitis.

The ear is affected in diabetes, the mastoid being the point of election. Large doses of quinin or phenacetin produce hyperemia in the labyrinthine mucosa, and deafness from exudates and increased tension. Hallucinations of hearing have been reported after large or long-continued doses of the salicylates, with probably the same lesions. Most hallucinations of hearing depend on irritation of the sound-perceiving organs and disturbances of the brain functions. The nerve is rarely irritated to its very termination in the cortex. Boilermakers' deafness depends on long-continued concussion of the auditory nerve, although the exposed condition of the workmen in this occupation may excite chronic catarrh of the middle ear with resulting labyrinthine changes. Men may work for years at beetling machines without labyrinthine symptoms, while those exposed for a while often suffer. Therefore, it is the intermittent exposure which causes pathologic changes in the labyrinth. Caisson-work produces hemorrhages in the middle ear, acute myringitis, hyperemia in the tympanum and labyrinth, and deafness. The lower convolutions of the cochlea are most affected. The pathologic sequence lies in the difference of pressure inside and outside of the ear during and after leaving the caisson. Gas-bubbles in the blood are also accused as pathologic agents.

Scarlatina has been already referred to in the paragraph on bacterial invasion of the ear, but additionally it may be remarked that after this exanthema sequestra often form, then exfoliate spontaneously or by surgical

interference, taking with them the cochlea, canals, internal meatus, and parts of the mastoid, exposing the dura mater, and leaving the ear totally deaf.

PANOTITIS.

The changes in panotitis consist in destruction and loss of substance of the soft parts, periosteum, and even of bone, throughout the entire tympanum, while the labyrinth may be seriously affected through the round window. The organisms of suppuration in the vessels, as well as in the tissues, have been reported during this disease. Necrosis may come on at an early date, bringing about rapid exfoliation of bone, or leaving behind for a time a sequestrum which, when finally carried off, proves to be a greater or less part of the labyrinth; or the entire region may be filled with neoplastic bone, taking the place of the capsule and its contents, with resultant total deafness.

DEAF-MUTISM.

Deaf-mutism depends on an internal otitis in early life from meningitis affecting the labyrinth along the aqueductus. The actual lesion is probably an infection of the perilymph, and defective circulation in the periosteum or even the entire district. If so caused, the apex of the cochlea is more likely to be affected than the lower part. According to other writers, deaf-mutism is always associated with nasopharyngeal disease. Others, again, attribute it to defect of the auricle with atresia of the meatus, to ossification of the windows, acquired defects in the nerve of hearing, prolonged disuse of the voice associated with moderate lesion of the conducting apparatus, with partial loss of hearing. Again, deaf-mutism may be motor, with preservation of hearing, defective mobility of the organs of speech; or motor and sensory, with ability to say a few words; or simply sensory, in which speech is heard but not understood.

All of these causes, separately or combined, lead to atrophy of the nerve, neoplasms in the labyrinth, atrophy of Corti's organ, ossification in the scalæ, loss of Reissner's membrane, and, finally, cases have been seen in which the ductus cochleæ and the scala vestibuli are opened into one cavity, and, in a word, there may be nearly total destruction of the labyrinth capsule. Proof that the labyrinth is very rarely wholly destroyed lies in the fact that most deaf-mutes have islands of high-pitched notes, which are not, however, useful for human intercourse. Acquired deaf-mutism depends on diseases before mentioned as likely to affect the labyrinth seriously in tender childhood, before any extensive vocabulary has been acquired.

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